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EDITORIAL

Some Historical Points

Because of the immense strides made in the practice of Paediatrics in the last 40 years or so, one is inclined to think of this specialty as a comparatively youthful member of the medical sciences. Even a cursory glance at its history should correct this impression.

The first printed book devoted to a single medical specialty was a text on child health written by Bagelardus, a German, in 1472. A 17th century English physician, Phaer, incorporated a text on paediatrics, "The Boke of Children," into a larger tome on physic called the "Regiment of Life" in 1645. Another text, "A Treatment on the Diseases of Children" by Michael Underwood was the accepted English reference work for 62 years from 1784 to 1846.

Of course, the Ancients had recorded much on the subject. Typical of the acuity of Egyptian clinical observation was the unvarying appearance of their god Horus in sculpture. He took the form of a sitting child with wasted legs—undoubtedly a case of cerebral palsy due to birth trauma.

Descriptions of rickets are particularly prevalent in the medical literature of the 17th and 18th centuries. Whistler in 1645 and Glisson in 1650 gave extremely accurate descriptions of the clinical features, but their contemporaries recommended such bizarre specifics as moss from dead men's skulls and church-bugs (possibly cockroaches) drowned in white wine. Bird in 1661 suggested in a treatise that "rekets" could be healed by the King's touch much the same as scrofula (cervical tuberculous adenitis). In 1780, some Dutch fishermen noted that cod liver oil would cure rickets completely, but it was not until 1820 that the standard English medical works would include this discovery, even with reservations. Also in 1780, a French physician noted in a discussion on the treatment of rickets that "the child should be stripped pitilessly and exposed to the rays of the sun."

Most of the paediatric literature of that era abounded with dissertations on infant feeding, including the seemingly age-old problem—breast versus artificial feeding. The abstinence of mothers from breast-feeding their babies might very well be considered a modern trend: on the contrary, a French councillor of state, Lenoir, writes in 1780: "One may estimate at from 20 to 21 thousand the number of infants born annually in Paris. One-thirtieth at the most are nursed at the mother's breast, an equal number is nursed in the parental home; two or three thousand, who pertain to the well-to-do class, are placed in the suburbs and surrounding territory with nurses of whose integrity the parents have assured themselves, and whose fees are greater on account of their proximity and their convenience."

In 1767, infant mortality was so alarming in England that an act of Parliament was passed, obliging parish officers of London and Westminster to send their infant poor to be nursed in the country. Before this measure was taken, 23 of every 24 children died in the poorhouses of London before they were one year old! Similar methods were practised in France during this time. Country girls were hired as wet nurses by travelling agents known as *meneurs* and *meneuses*. These agents also arranged for the city clients' babies to be taken with the nurses to the country. Laws prevented the *meneur* from transporting the infants *alone* in open wagons for long and jolting journeys—a practice apparently to be curtailed at that time.

No less than 500-600 Parisians were jailed yearly for failing to pay their infants' wet nursing fees. Although most of these nurses were poorly paid, badly treated, and often diseased, a select few were retained in handsome fashion as nurses to royal infants. One, a Madame Mercier, the nurse to Louis XV, was created a noble in 1716 for her services.

Many medical savants of the day cried out against the practice of wet nursing in favour of either maternal nursing or artificial feeding. One authority stated in 1786 that there were "dangerous consequences which result from the nursing of infants by wet nurses. These nurses are for the infants the cause of diseases of which they take the principle with the milk. The infants develop the vices of the wet nurses, they become extremely inclined to wine. The infants become infected with skin and venereal diseases and have been known to develop scurvy and stone. . . ."

Without the support of present-day evidence, Michael Underwood stated in 1784: "Every infant should be nursed by its own mother, when not contraindicated by reasons of health. . . . In 99% of cases the mother's milk will agree with the child. . . ."

Those who denounced the use of milk of any kind—and at that time there were many—would recommend the use of one or both of two very old mixtures. One was *pap*, which consisted of bread, preferably 3 to 4 days old, mixed with sugar and cooked in water, beer, or wine, to the consistency of mush. The other was *panada*, which was a slightly more complex mixture including broths of legumes and butter. It was not uncommon for the child to be fed up to *two quarts* of pap a day, most of which was promptly regurgitated. The utensils used for feeding these mixtures were interesting. One (pictured) is a deep boat-like spoon with cover, feeding opening, and hollow handle. It is reported that the contents of the spoon were not infrequently blown into the reluctant child's mouth through the handle.

When thoroughly absorbed with history as interesting as this, one could go on and on, tracing the quaint and fascinating steps to the present—but unfortunately space does not permit us to do so.

The Editor is indebted to Dr. T. G. H. Drake, former Senior Physician at the Hospital for Sick Children, for the use of material from his excellent collection of Paediatric History, which is no doubt familiar to many of our readers.

CANCER IN INFANCY AND CHILDHOOD

W. H. SHAW, 5T5

IN recent years, cancer has emerged as one of the great killers in childhood. Since 1950 in Ontario it has ranked second only to Accidents and Violence as a cause of death in the 5-14 year-old group.[1] This is doubtless a result of the advent of antibiotic therapy and the resultant decline in the mortality due to infectious diseases.

Cancer in infancy and childhood may well be discussed as a single entity since it differs from cancer in adulthood in a number of significant ways. Whereas carcinomata constitute the bulk of malignant tumours later on, in early life there is a great preponderance of sarcomata.[2,3] Many of these are classified as "embryonic", a type virtually never seen in adult life. Generally speaking, childhood cancer is characterized by rapid growth, early and widespread metastasis, and a high mortality rate.[3,4,5,6] Weight loss, anemia, and cachexia, so frequently seen in adult cancer, are the exception in childhood malignancy, and then only terminal events.[5,6] Occasionally juvenile cancer exhibits a disconcerting disparity between its histological appearance and its clinical course.[3,5] For these and many other reasons childhood cancer is best discussed as a separate subject.

The four most common types of cancer seen in early life are (i) leukemia and the lymphomata, (ii) central nervous system tumours, (iii) cancers of the kidney region, and (iv) cancers of bone. Within the short span of infancy and childhood, each of these main types has a period of a few years in which the bulk of cases appear. Thus, cancer of the kidney region occurs most frequently in infancy and early childhood, leukemia in early childhood, and intracranial tumours in mid-childhood, while bone cancers, which begin to appear in late childhood, are most common in adolescence. The resultant curve of age incidence exhibits its peak within the first five years, declines during childhood, levels off before puberty, and begins to rise again early in adolescence. The relatively lower incidence around 10-12 years of age is probably best interpreted as the point of intersection of the declining curve of the growths peculiar to childhood and the rising curve representing typical but early cases of growths common in adults.[2]

Leukemia and the Lymphomata

Leukemia

Leukemia is by far the most common form of cancer in childhood. Although its pathogenesis is still a matter of dispute, most authorities consider it a malignant neoplasm. The acute form of leukemia is customary in childhood; the cell-type is usually so undifferentiated that further classification as "myelocytic", "lymphocytic", etc., is impossible. The majority of cases occur within the first five years of life, the peak incidence being at four years of age. Males are affected more commonly than females.

The primary pathological change is an extensive uncontrolled proliferation of leukopoietic tissue. This occurs in many sites in the body—most notably lymph nodes, spleen, bone marrow, liver and kidneys. Leukemic replacement of bone marrow depresses the formation of normal elements, resulting in anemia, granulocytopenia and thrombocytopenia.

The onset of acute leukemia may be insidious or abrupt; it may present in a number of ways. Most commonly there

is gradual development of pallor, fatigue or anorexia—evidences of anemia. However, hemorrhagic manifestations such as bruising, epistaxis, or even hematuria are frequently the first clinical effects of the disease. Bone or joint pain (due to leukemic infiltration) is sometimes the initial complaint: it may be localized, or more widespread in distribution. Often acute leukemia resembles a fulminating infection at its onset, with the abrupt appearance of high fever and prostration. Many of these common presenting complaints are prominent in the subsequent course of the disease.

Lymphadenopathy is frequently found early, but is rarely conspicuous. Superficial nodes are discrete and rubbery; they are non-tender, unless draining an infected area such as the mouth. Enlargement of mediastinal nodes may produce pleural effusion, or cough and dyspnoea. Splenomegaly is a customary and early sign; the spleen is typically soft and usually not strikingly enlarged. Hepatomegaly is frequent. In addition to the skin and mucous membranes, bleeding may occur in a variety of other sites. Retinal hemorrhage is not uncommon, and neurological disturbances (due to hemorrhagic and leukemic involvement of the central nervous system) appear on occasion. Stomatitis and pharyngitis are relatively unusual events.

Early clinical diagnosis often depends on the differentiation of this condition from other possible causes of anemia, purpura, bone pain and arthralgia, lymphadenopathy and hepatosplenomegaly. X-ray studies may reveal mediastinal and osseous involvement. Examination of the peripheral blood commonly reveals normochromic anemia, marked thrombocytopenia, and a leukopenia most marked in the granulocytic series. More significant, however, is the high percentage of immature and abnormal leukocytes. Final diagnosis should follow bone marrow examination, which typically reveals great preponderance of immature leukocytes with marked depression of megakaryocytes and erythrocyte precursors.

Aminopterin and ACTH (or Cortisone) are currently the main drugs used in the treatment of acute leukemia, and are often used in combination. X-irradiation is indicated only to shrink enlarged glands which have been producing local pressure symptoms.

The prognosis is uniformly hopeless. Temporary remissions (during which clinical and laboratory evidences of the disease vanish) are common under current therapy, but may occur occasionally in untreated cases. Invariably, however, progressive deterioration resumes, terminating in death (usually due to massive hemorrhage or overwhelming infection) within a few months in most cases.

Chronic leukemia is rare in childhood. It is always myelocytic in type. Symptoms are slower in onset, and are usually referable to anemia and massive splenomegaly. Treatment consists of X-irradiation (usually of the spleen) and/or chemotherapy (Urethane or Myleran). Although the course is more prolonged than in acute leukemia, the prognosis is equally hopeless and spontaneous remissions are rarer.

LYMPHOSARCOMA

Lymphosarcoma is closely related to lymphatic leukemia, in fact they may be variants of the same disease entity. It is less common than leukemia and may be found at any age.

The basic disturbance is an overgrowth of lymphocytes of varying maturity within lymph nodes. Initially it is localized to one node or group of nodes, which become enlarged and adherent to adjacent tissues. Sometimes, however, it appears to begin at a number of sites simultaneously. It inevitably spreads to

involve all nodes and other lymphoid tissue in such locations as spleen, gastro-intestinal tract, and bone marrow. Ultimately there is invasion of such organs as liver, heart and kidneys. The picture may rapidly become indistinguishable from acute leukemia, with leukocytosis and abnormal lymphoblasts in the peripheral blood.

The clinical onset of the disease depends on the initial lymph node involvement. If superficial, it may appear as progressive enlargement of cervical, axillary or inguinal groups. If mediastinal, symptoms due to cardiac or respiratory embarrassment may present. Enlargement of abdominal glands may produce pain, and later on ascites or intestinal obstruction. Systemic effects ensue — fever, fatigue and wasting. Hepatosplenomegaly becomes obvious. With terminal bone marrow involvement, the clinical picture of acute leukemia may supervene.

Definite diagnosis is usually obtained by biopsy of several suspicious glands. X-ray studies may reveal abundant lymphoid tissue in chest, abdomen or bones.

The treatment of choice is surgical excision where possible i.e., (when localized to a single group of nodes), followed by X-irradiation. Nitrogen mustard may be used instead of radiotherapy or when the disease is too widespread for radiotherapy to be practicable.

The prognosis is grave although apparent cures occasionally occur.

HODGKIN'S DISEASE

Hodgkin's Disease is another important, usually fatal disease of lymphoid tissue. It is generally regarded as a neoplastic condition, although dispute on this point persists. It occurs much more frequently during the school-age period than in infancy, and most patients are males.

The disease process begins in the lymph nodes, and consists of a reticulum-cell proliferation with a subsequent tendency to fibrosis. Usually superficial nodes (particularly cervical) are first involved, but the process spreads to spleen, liver and lymphoid tissue throughout the body.

The initial evidence of Hodgkin's Disease is usually painless asymmetrical enlargement of the cervical lymph nodes. Soon axillary and inguinal lymphadenopathy is noted. The enlarged glands are at first soft and rubbery in consistency, later becoming increasingly hard and fibrous; they remain discrete. The spleen commonly becomes palpable. Involvement of mediastinal and abdominal nodes results in symptoms due to pressure on adjacent structures: these may become very distressing. As the disease progresses constitutional effects such as weakness, weight loss, and fever (sometimes Pel-Ebstein in type) become increasingly more marked. Ultimate involvement of kidneys, abdominal viscera or bones may cause a wide variety of symptoms. The terminal phase is marked by progressive anemia and cachexia.

Early diagnosis must exclude other lymphadenopathies. Biopsy of an enlarged gland gives positive identification.

If a single group of nodes is affected surgical removal is indicated. When more than one group is involved, irradiation of all affected regions may be tried. Generalized disease is probably best treated with a Nitrogen Mustard such as TEM. Hodgkin's Disease is usually fatal, but months or even years of relatively normal life may be attained.

EMBRYONIC TUMOURS

The members of this important group appear almost exclusively during infancy and early childhood—occasionally they are found at birth. Histologically, they

are not merely anaplastic but truly embryonic, resembling their parent tissues at very immature stages of development. Regarding etiology, Willis[8] says "Most of the ordinary tumours of adult life arise only after prolonged exposure of the tissues to carcinogenic chemical substances or other agents. This cannot apply to embryonic tumours; they arise during actual organogenesis from tissues still immature. The causes of these growths . . . must be very different from those of adult tumours; they must be sought in . . . disturbances in metabolism and maturation of growing tissues". Other authors,[4,7,9] however, feel that these tumours probably arise from Cohnheim "rests" of superfluous embryonic tissue. Heredity is a significant factor only in the case of retinoblastoma.

NEPHROBLASTOMA

Nephroblastoma, or Wilms' tumour ("malignant embryoma of kidney"), is one of the most common malignancies of infancy and early childhood. It is occasionally found at birth, and is rare over five years of age. Wilms' tumour is almost invariably unilateral, both kidneys being affected with equal frequency. Its source is immature renal mesenchyme, which may constitute the bulk of the growth histologically. In addition, there is often a variety of renal epithelial structures, plus mesenchymal elements such as muscle, cartilage, myxomatous or adipose tissue; this variegated picture gave rise to the names "adenosarcoma" and "mixed tumour".

Grossly, the growth remains encapsulated until late in the course of the disease; local extension involves the adjacent kidney tissue, perirenal fat and pelvic veins. Metastasis is blood-borne and occurs relatively early to lungs, brain, liver and bone.

Clinically, the first evidence of nephroblastoma is usually (⅔ of cases) a painless abdominal mass—either a progressive swelling noted by the parents, or a tumour discovered by the doctor during a routine examination. Occasionally the mass is painful. Anorexia, or nausea and vomiting are fairly frequent complaints; feverishness, weight loss, pallor and fatigue are sometimes noted. Hematuria is infrequent, and other urinary symptoms even more so. The tumour is palpable as a firm non-tender mass, which may extend to the midline (which it does not usually cross) and down into the iliac fossa.[10] Leukocytosis and anemia are often found.

Preliminary investigation should include pyelograms to determine the size and nature of the growth (distortion of the renal pelvis is a characteristic finding), and the condition of the other kidney. Chest X-rays must be taken to detect lung metastases. These studies should occupy no more than a day or two, during which period the abdomen should be examined only by the individual responsible for the management of the case.

Nephrectomy at the earliest possible moment is the treatment of choice; it is followed by a course of radiotherapy. Preoperative irradiation is performed only when the tumour is too large for immediate removal to be a safe procedure.[11] The prognosis is grave, but not hopeless. Survival for two years or more following operation is considered a probable cure. Recent reports have claimed cure rates varying from 14 to 47 per cent. The cure rate is markedly higher with patients below 12 months than with those above that age.[11]

NEUROBLASTOMA

This important tumour occurs most frequently in infancy and early childhood, but may present at birth or (occasionally) in adult life. It is derived from undifferentiated neuroblasts of the sym-

pathetic nervous system. Approximately half of all cases arise in the adrenal glands (medulla) or their immediate neighbourhood; the rest are found elsewhere in the sympathetic chain—retroperitoneally in abdomen or pelvis, in the posterior mediastinum, or in the neck. Bilateral primary adrenal growths occur infrequently.

This is a highly malignant tumour which metastasizes early and widely. The skeleton (particularly the skull) and the liver are the most common sites of secondaries, also local lymph nodes and lungs. While the tumour is encapsulated initially, sooner or later it extends locally, involving liver, large vessels, pancreas, kidneys, etc.

The most common single presenting sign of neuroblastoma is an upper abdominal mass.[10] It is the symptoms due to metastases, however, which dominate the clinical picture; frequently they appear while the primary growth is still inconspicuous. Skull deposits may be prominent (Hutchison syndrome), and frequently involve the orbit, producing unilateral exophthalmos. Liver involvement results in massive hepatomegaly (Pepper syndrome). These two main syndromes so frequently overlap that the terms are rapidly falling into disuse. Less prominent symptoms of spread of the growth are pain in the extremities and hematuria. Fever and leukocytosis may be present. Secondaries in the long bones have been mistaken for Ewing's tumour.

In the absence of striking metastatic phenomena, the clinical picture may suggest Wilms' tumour. The neuroblastoma may extend across the midline, or produce marked displacement of the kidney on the affected side (as revealed by pyelogram)—unusual findings in nephroblastoma. Preliminary investigation should include X-ray studies of skeleton and lungs to detect spread to these sites.

The treatment of choice is surgical removal of the primary tumour, and postoperative irradiation of the site. Liver involvement is not a contraindication; some authors[5,10,13] recommend this therapy even in the presence of osseous metastases. Chemotherapy (Aminopterin, Nitrogen Mustard, ACTH or Cortisone) may be of help; interesting results have recently been reported with the use of Vitamin B_{12} intramuscularly.[12]

The prognosis is grave. Untreated, the tumour almost invariably kills within a few months. The results of therapy have been improving recently: ¼-½ of cases surviving 3 years or longer.[5,10] Prognosis appears to vary with age, the earliest-appearing usually being the most speedily fatal. Spontaneous cure is extremely rare, but may occur, due either to maturation into benign ganglioneuroma,[8,10] or to hemorrhage and necrosis within the tumour.[12]

MEDULLOBLASTOMA

This is almost certainly a truly embryonic tumour derived from still-immature neutral tissues before or shortly after birth.[8] It will be discussed in the section on intracranial tumours.

RETINOBLASTOMA

This is a relatively rare tumour which is virtually restricted to infancy and early childhood; it probably originates in utero,[3,10] and may present at birth.[14] While many victims exhibit an inherited liability to the disease, the majority are apparently sporadic. In 25-30% of cases, independent primary growths arise in both eyes, usually separated by an interval of several weeks or months. The tumour begins in the posterior part of the retina usually, and may spread subretinally (detaching the retina), or extend forwards into the vitreous. Involvement of the ciliary body produces pupillary dilatation and glaucoma. The

growth may perforate the sclera and fill the orbital cavity, producing proptosis and eventually protrusion of the large fungating tumour mass. More significant is spread via the optic nerve into the cranial cavity where the tumour will speedily extend in the subarachnoid space. The important early diagnostic signs are dilatation of the affected pupil, a white or greyish reflex, or a squint.

Treatment consists in enucleation of the involved eye with removal of as much of the optic nerve as possible; the severed end should be examined microscopically for malignant infiltration. Surgery must be followed by periodic ophthalmoscopic examination of the unaffected eye for several years. Bilateral involvement where vision is still present in one eye is probably best treated by enucleation of the blind eye and irradiation of the other. The crucial factor in prognosis is the extent of spread of the tumour along the optic nerve. Recent series have reported 50-85% recoveries.[3,5,8] Spontaneous cure (by necrosis within the tumour) occurs rarely.

HEPATOBLASTOMA

Rarely is the liver the primary site of an embryonic cancer. Most cases occur in infancy. Histologically the tumour parallels nephroblastoma in its preponderance of epithelial and mesenchymal elements in varying proportions, plus various heterotopic tissues. There is usually a history of increasing abdominal distention, and often vomiting. The enlarged liver mass feels firm and nodular. Although patients tend to come under observation before metastasis has occurred, the prognosis is poor. Surgical excision may give better results than deep irradiation alone.

RHABDOMYOSARCOMA

This uncommon tumour consists of embryonic mesenchymal tissue exhibiting varying degrees of cross-striation. It is usually either a growth derived from immature or undifferentiated tissue, or part of a mixed tumour consisting of several mesenchymal derivatives.[8] The commonest sites are: tongue, soft palate, bladder, prostate, spermatic cord and epididymis, vagina ("sarcoma botryoides"), and cervix uteri. Rhabdomosarcomata in these sites usually appear during childhood. The results of treatment of these highly malignant growths have been very discouraging.

Intracranial Tumours

Intracranial cancer is the second most frequent type seen in childhood.[5] It differs from its adult counterpart in two important respects: (i) the expansible nature of the skull during infancy and childhood, and (ii) the fact that more than ⅔ of the tumours are infratentorial. The two most common types are astrocytoma and medulloblastoma, both of which are predominantly cerebellar in location.

Being neither visible nor palpable, intracranial growths offer an extra challenge in diagnosis. Their presence and nature must be deduced if possible from indirect clinical evidence, and from special techniques such as skull X-rays, ventriculography, pneumencephalography (contraindicated in the presence of increased intracranial pressure), and angiography.

ASTROCYTOMA

Astrocytoma is the most common intracranial neoplasm in childhood. It occurs most frequently around 9 years of age, and usually arises in the vermis of the cerebellum. The tumour is relatively benign and slow-growing; it characteristically breaks down, forming a cystic cavity with the growth as a part of its wall. Although the astrocytoma originates in the midline, its cyst extends

laterally into one or other hemisphere, producing a predominantly unilateral picture of cerebellar disturbance. As tumour and cyst slowly enlarge they impinge upon the circulation of cerebrospinal fluid, producing internal hydrocephalus and clinical evidence of intracranial hypertension.

Typically, there is gradual onset of headache and vomiting. Slowly progressive enlargement of the head and the signs of cerebellar dysfunction appear subsequently. The latter are usually confined to the same side of the body as the tumour, and include: muscular flaccidity or atonia, asthenia, ataxia and nystagmus. A squint may develop, due to external rectus paralysis.

Treatment consists in evacuation of the fluid from the cyst and excision of the growth in its wall; if performed early this yields complete and permanent cure in a majority of cases. Prognosis is worsened if the tumour involves vital centres, or if there has been long-standing intracranial hypertension.

MEDULLOBLASTOMA

Medulloblastoma, an "embryonic" cancer, is slightly less frequent than cerebellar astrocytoma.[8] It is most common around 6 years of age, and affects males more frequently than females. The usual site of origin is the vermis (and hence the midline) in the roof of the fourth ventricle. The tumour is highly malignant, rapidly growing, and has a marked tendency to spread in the leptomeninges, which may carry it over the brain and down the spinal canal. Expansion of the growth results in internal hydrocephalus and the symptoms and signs of increased intracranial pressure.

The clinical course typically begins with headache and vomiting, most marked on arising in the morning. Soon the patient becomes listless, and within a few weeks a little unsteady on his feet. By this stage progressive enlargement of the head has probably been noted; in younger children, whose skulls are more readily distensible, headache is milder and enlargement of the head may be the first sign of the disease. As equilibrium deteriorates, the gait becomes stumbling and the child has frequent falls; ultimately he may be completely unable to walk. Visual impairment is usually present—due to a squint or to failing visual acuity. Marked weight loss often results from the continued vomiting. A series of opisthotonic seizures is climaxed by the death of the patient, some 6-8 months after the onset of symptoms.[15]

The combination of headache, vomiting, unsteady gait, and enlargement of the head (with a "cracked-pot" percussion note) should suggest the diagnosis. Clinical differentiation from astrocytoma is often impossible, although the latter condition is characterized by slower development of symptoms, more unilateral evidence of cerebellar disturbance, and more frequent occurrence of nystagmus.

Surgical exposure of the growth is necessary for positive histological diagnosis, but complete excision of a medulloblastoma is virtually never achieved.[10] The best treatment appears to be X-irradiation of the entire brain and cord as soon as possible after surgical exploration. Results have generally been discouraging;[5,10,15,16] however, a recent series treated in Manchester has yielded well over 50% three-year survivals.[17]

GLIOMATA OF THE BRAIN-STEM

At least 20% of intracranial tumours in childhood are brain-stem gliomata;[10] their usual site is the pons, infrequently the medulla or the midbrain. The clinical picture is usually the result of destruction of one or more cranial nerve nuclei (frequently the sixth), commonly bilaterally. Involvement of cerebellar or pyramidal tracts in the brain-stem may

occur. Headache is unusual, intracranial hypertension being minimal or absent in this condition. However, vomiting may occur and may even lead to wasting. The presence of a low grade fever has often led to the erroneous diagnosis of encephalitis. The prognosis is hopeless, since their location makes surgical removal of these gliomata impossible. Occasionally X-irradiation gives temporary symptomatic relief.

SUPRATENTORIAL TUMOURS

Supratentorial tumours in childhood occur largely in the region of the third ventricle. Depending on their locations they produce varied clinical pictures: internal hydrocephalus, or effects due to pressure on the hypophysis (hypopituitarism), the optic chiasm (bitemporal hemianopia), or the hypothalamus (diabetes insipidus, genital dystrophy, somnolence and obesity). Pinealoma may be associated with precocious sexual and somatic development. Although in most instances surgical excision offers the only hope of cure, their locations frequently render this impracticable.

Bone Sarcomata

Primary bone cancer is not infrequent in late childhood, although its peak incidence falls during adolescence. The two most common types are osteogenic sarcoma and Ewing's tumour.

OSTEOGENIC SARCOMA

Osteogenic sarcoma is the most malignant cancer of bone. The majority of cases occur over 10 years of age, and males are affected slightly more often than females. Almost invariably the tumour originates in the metaphysis of a long bone, the most common sites being: lower end of fermur, upper end of tibia, upper end of humerus, and upper end of fibula. More than half are found around the knee. Less usual locations are pelvis and scapula. The growth arises from osteoblastic tissue; it extends locally both inwards to fill the medullary cavity, and outwards to the periosteum, beneath which it expands and forms varying amounts of osteoid tissue and true bone. Frequently this "tumour bone" is laid down in spicules perpendicular to the shaft, giving a radiographical "sun-ray" appearance. With perforation of the cortex, growth may invade adjacent soft tissues. Metastasis is chiefly to lungs, and occurs early.

The first symptom is persistent pain locally, followed after a variable period (often several weeks) by the appearance of a palpable tumour mass, which develops into a bulbous enlargement at the end of the long bone affected. Function of the limb is usually impaired. The consistency of the swelling varies from soft to hard, depending on its content of bone. Occasionally fever is present. Pathological fracture at the tumour site is a late occurrence.

Diagnosis rests on the combination of clinical, radiographic and histological findings. Elevation of the serum alkaline phosphatase is not uncommon. Investigation of any case must always include chest X-rays to detect secondaries. Since treatment consists of amputation of the involved limb, preoperative diagnosis should be as positive as possible. In the presence of pulmonary metastases cure is impossible, but amputation may be advisable to relieve local pain. The prognosis in osteogenic sarcoma is extremely grave, the postoperative five-year survival rate being 15-20%; in children the figure is probably even lower.

EWING'S TUMOUR

Ewing's tumour is rarer than osteogenic sarcoma, and has a somewhat lower age incidence (majority between 5 and 20 years of age). The usual site is the shaft of a long bone: tibia, femur,

humerus and fibula most frequently. Clavicle, os calcis, ribs and flat bones are not uncommon locations, however. The histiogenesis of Ewing's tumour is not known for sure. Growth probably begins in the medullary cavity and extends longitudinally and laterally. As the tumour invades the cortex, it stimulates the laying-down of successive layers of new (normal) bone beneath the periosteum, resulting in a laminated "onion-skin" appearance on X-ray. Metastasis is usually to the lungs and to the other bones.

The clinical picture resembles that of osteogenic sarcoma, although in Ewing's tumour fever is frequent and may lead to the erroneous diagnosis of acute osteomyelitis. The growth is often indistinguishable, even histologically, from a bony metastasis of neuroblastoma.

Treatment begins with a course of X-irradiation, to which Ewing's tumour is markedly sensitive. Rapid shrinking of the swelling makes its identity more certain. Following radiotherapy, amputation or resection is performed, if the site of the growth permits. The prognosis is probably slightly worse than in osteogenic sarcoma.

Soft-Tissue Sarcomata

The sarcomata of the soft tissues constitute a group whose importance is too often underestimated.[9] They can appear at any time during infancy and childhood, and have been reported at birth. These growths arise from mesenchyme and exhibit all degrees of maturation into nerve sheath, fibrous and adipose tissue, and skeletal muscle. The most mature forms (viz., neurolemmoma, fibroma, lipoma, and rhabdomyoma) are benign growths, while their incompletely differentiated counterparts are usually highly malignant. Many soft-tissue sarcomata are so immature that they cannot be labelled specifically, and must be classed as "of uncertain origin."[9] Metastasis is typically blood-borne.

These growths are commonly situated superfically, where they may be felt as solid lumps in or beneath the skin, or in skeletal muscle.[9] Clinical distinction between benign and malignant forms is usually impossible; consequently any such mass must be regarded as malignant and treated by wide surgical excision. The resected tissue should be examined histologically to determine its nature and to check the adequacy of its removal.

Fibrosarcoma may arise from connective tissue anywhere, but is most common in the extremities, particularly the lower. Its consistency varies from hard to soft and friable, depending on the proportions of fibrous and cellular tissue it contains. Generally speaking, the softer and more cellular the tumour, the greater is its malignancy.

Neurofibrosarcoma (neurogenic sarcoma) may arise in obvious relation to nerves, or if not, its neurogenous origin can often be demonstrated histologically. It may arise as a solitary dermal or subcutaneous lesion, or less commonly from one of the multiple tumours of von Recklinghausen's Disease. Frequently neurofibrosarcomata are indistinguishable from fibrosarcomata—a fact which has led to much dispute regarding their histiogenesis.

Liposarcoma is more common in later life than in childhood.[8] Its most common sites of origin are the lower limbs, buttocks, and retroperitoneal tissues.

Rhabdomyosarcoma is occasionally found in skeletal muscle: most such cases have occurred in children.[8]

Malignant Teratoma

In most parts of the body teratomata are almost invariably benign, in other areas they are usually benign, while in

a few situations (notably the testis) they are almost always malignant. The chief sites of malignant teratomata are: sacrococcygeal region (presacral in origin[12]), testis, ovary, anterior mediastinum, retroperitoneal tissues, and within the cranium. Gonadal and mediastinal growths are most commonly found in young adults, but may arise earlier. Those in the other sites nearly all present at birth or during childhood. A previously-noted benign tumour may undergo malignant change at any age. Generally speaking, malignant teratomatous tissue is solid, in contrast to the cystic structure usual in the benign variety.

A superficially located growth will be detected without difficulty, especially if it is enlarging; a deeper growth will probably reveal itself by symptoms due to local extension or distant metastasis. Any suspicious lump should be speedily and thoroughly excised and examined histologically: even if benign, a teratoma is potentially dangerous.

Carcinoma

Carcinomata form but a very small fraction of the malignant tumours of infancy and childhood—3-10% according to various series.[3] In further contrast to cancer in adult life, only occasionally does carcinoma in childhood arise from the skin or gastrointestinal mucosa.[9] More common sites are testis, ovary, thyroid and liver. Pathologically, childhood carcinoma resembles its adult counterpart, and is treated similarly.

Conclusion

Cancer has recently emerged as a leading cause of death in early life. The most important malignancies of childhood are more or less confined to that period. Increased vigilance, and knowledge of their peculiarities would result in more prompt treatment of childhood cancers, and a considerably lower mortality rate.

Acknowledgment

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SCURVY

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SCURVY is a deficiency disease due to a lack of vitamin C (ascorbic acid). It occurs mainly in infants but can be found in older children and adults.

Aetiology

Scurvy, under normal conditions, is limited to artificially fed infants. Breast milk contains 4-7 mgms. of ascorbic acid per 100 c.c., which is sufficient to supply the daily requirements of a growing child. Rarely, a mother's diet may be deficient in vitamin C with a resulting lack of ascorbic acid in the breast milk, and scurvy can occur in these children.

The prophylaxis of scurvy has been known for years and, yet, cases still occur. These result from a lack of knowledge on the part of the mother about adequate vitamin administration. Most mothers give their infants orange juice, multiple vitamin preparations, or ascorbic acid tablets from 2-4 weeks after birth.

In discovered cases of scurvy the reason is usually one of the following:

1. Failure to give vitamin C in any form.
2. Feeding the child orange juice which has been boiled. Boiling is believed to destroy the vitamin C content of orange juice, especially in an alkaline medium.
3. Mothers attempt to make the orange juice more palatable by adding sodium bicarbonate (baking soda), which decreases the ascorbic acid content.
4. Vomiting, diarrhoea and various non-specific skin rashes have been attributed in most cases unjustly, to orange juice, and thus it may be discontinued by the mother without the doctor's knowledge.
5. Rarely, scurvy may result from chronic gastro-intestinal disease, where juices, fruits and vegetables have been discontinued.

Incidence

In 1953, 4 cases of scurvy were reported at the Hospital for Sick Children. In 1954 over 50 cases have been treated.

Why has there been such a startling increase in scurvy in 1954? The answer to this is not known. It may be due to the above mentioned factors plus better diagnosis, or it may be due to some as yet unknown factor. It seems hard to conceive that mothers have suddenly stopped giving vitamin C. One fact is certain; there is a yearly irregularity in the incidence of scurvy, which cannot be completely explained.

Scurvy in the newborn period is very rare since the fetus obtains adequate vitamin C from the mother before birth. It takes at least 3 months of a deficient vitamin C intake to produce frank evidence of scurvy. The usual age distribution is 5-18 months with a peak at 9 months. Scurvy can occur in older children and adults, but is uncommon under normal conditions.

Pathogenesis

Vitamin C cannot be synthesized in the body and, therefore, it must be supplied in food. Vitamin C is necessary to form the normal structure and function of intercellular substance. Since collagenous tissue is present in all parts of the body, scurvy is a generalized disease. The main manifestations of the disease are due to involvement of the collagen

of intercellular substance of blood vessels, the matrix of bone, and the dentin of teeth. In the blood vessels the result is haemorrhage. In bone there is generalized osteoporosis. Ossification ceases, and calcified cartilage piles up at the epiphyseal plate instead of new bone. This causes the "white line" so characteristic on the X-ray. Osteoblasts fail to form osteoid tissue and the calcified cartilage remains. Subperiosteal haemorrhages occur, which cause the severe bone pain in children suffering from scurvy. This is most common at the knee. The dentin of teeth is resorbed, pulp changes take place, rarefaction of alveolar bone occurs with the subsequent loosening of the teeth.

Clinical Picture

In the early stages of scurvy, the child becomes irritable, develops anorexia and vague digestive disturbances. The irritability becomes more marked, and the child cries on being picked up, changed or bathed and stops when put down and left alone.

The child's legs become very tender and painful. The pain causes lack of movement and possibly a pseudo-paralysis. The child will draw up its legs into a position of flexion or assume the typical "frog position" with semi-flexion and external rotation of the hips and semi-flexed knees. The child resists any attempt at straightening of the legs. Swelling may occur over arms and legs, especially at the knee. These are due to subperiosteal haemorrhages.

Bleeding manifestations are usually present. Petechiae can occur in the skin; purpuric spots are noted on the gums which are purplish and swollen. Mild trauma may result in large ecchymosis. Hematuria, hematemesis, melena also occur. Exophthalmus may be noted, due to periorbital haemorrhage and more rarely, intra-cranial haemorrhage can occur.

Palor is usually noted, due to a secondary anaemia which is microcytic and hypochromic but occasionally is macrocytic with a megaloblastic marrow.

The characteristic *scorbutic rosary* is usually present early. This is due to a subluxation of the sternal plate at the costo-chondral junction causing a sharp step up as the hand is passed laterally over the chest. In rickets the junction is more rounded. Pain on respirations may occur, leading to rapid shallow breathing.

General manifestations of fever, failure to gain or loss of weight are usually present.

Diagnosis

This is based on a characteristic history of poor or deficient intake of vitamin C, the typical physical findings, plus X-ray and laboratory tests.

The normal ascorbic acid level in plasma is 0.6-1.0 mgm/100 c.c. In scurvy the level is always zero. In latent scurvy the levels may also be low or zero.

The X-ray shows several characteristic signs:

1. Diffuse osteoporosis.
2. The "white line" of calcified cartilage of the epiphyseal plate.
3. A zone of rarefaction under the "white line" which may be complete, or just show a triangular area at the edge of the bone resembling a fracture. This is called the *Corner Sign*.
4. The secondary epiphysis shows a white halo of calcified cartilage around an osteoporotic centre.
5. There may be a slipped epiphysis. This heals with treatment without reduction. During the healing phase the subperiosteal haemorrhages be-

come calcified and are seen on the X-ray.

If the diagnosis is in doubt, a therapeutic trial of vitamin C may establish the diagnosis. There is rapid relief of symptoms.

The differential diagnosis includes arthritis, poliomyelitis, rickets and blood dyscrasias. Their differentiation is usually not difficult.

Prevention

Scurvy can and should be prevented. The daily requirements for infants up to 3 years is 30-35 mgm of ascorbic acid which is provided by 2 ounces of orange juice, or 6 ounces of tomato juice, or in any of the recognized synthetic preparations, the simplest being 50 mgm of ascorbic acid, dissolved in a teaspoonful of water. Orange juice should be started between 2-4 weeks. At first 1-2 teaspoons of orange juice are diluted in 1 ounce of cooled, boiled water increasing the amount gradually until 2 ounces of juice are given daily. The water should be boiled and cooled before the orange juice is added. Some paediatricians recommend that orange juice be postponed until 6 months, since the child is less likely to refuse it then. If the child refuses the juice, has persistent vomiting or loose stools, ascorbic acid or multivitamin preparations may be used.

The nursing mother should have 150 mgm of ascorbic acid daily, or 8-10 ounces of orange juice.

Treatment

The treatment of scurvy is simple. 100-300 mgm of vitamin C are given daily. At the Hospital for Sick Children half is given as orange juice and half as ascorbic acid or multi-vitamin drops.

The response is excellent. In 24-48 hours the infant is less irritable and the legs are less tender. In 48-72 hours the gums show healing and in 10-14 days there is X-ray evidence of deposition of new bone. Body growth is quickly resumed and any deformity rapidly disappears.

There are no effects of overtreatment, fulfilled, any excess vitamin is excreted in the urine. It is important to realize that vitamin C is not stored and must be supplied daily.

Acknowledgment

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RICKETS

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RICKETS may be defined as a general disorder of metabolism affecting chiefly the bone-forming minerals, calcium and phosphorus, and manifesting itself by poor calcification of bone.

Classification of "Rickets"

1. simple rickets
   (a) Vitamin D deficiency
   (b) Absorption defects
   e.g. Coeliac Rickets
2. primary hyperparathyroidism (with or without secondary renal insufficiency).
3. rickets due to renal abnormalities
   A. Pan-nephritis (so-called "renal rickets") combined glomerular and tu-

bular lesions (with or without secondary hyperparathyroidism).

e.g. 1. Chronic glomerulonephritis.
2. Chronic pyelonephritis.
3. Renal hypoplasia.

B. Primary Renal Tubular Dysfunction.

1. Vitamin D Resistant Rickets—simple form.

2. de Toni-Fanconi-Debré Syndrome (hyperphosphaturia, Vitamin D resistant rickets with aminoaciduria).

3. Cystinosis or Cystine Storage Disease (de Toni-Fanconi-Debré syndrome plus tissue deposition of crystalline cystine).

The following discussion will be limited to Simple Rickets. However, any child or adult showing radiological signs of rickets not due to hyperparathyroidism or to chronic renal disease, and who does not respond to normal therapeutic doses of vitamin D should be labelled Vitamin D resistant. Though comparatively rare, Vitamin D resistant rickets is definitely a problem in management and physicians should remain aware of the condition.

Aetiology

Rickets may develop because of the lack of either of two factors:

1. Sufficient exposure to ultraviolet light.
2. Adequate amounts of vitamin D.

If either of these is present in sufficient quantities, rickets will not develop; either one by itself will produce a cure. Human skin contains 7-dehydro-cholesterol, a provitamin D 3, which becomes activated in the presence of ultra-violet rays of the sun. The resulting product is natural vitamin D, a potent antirachitic factor.

Ultraviolet Rays Sunshine contains ultraviolet rays, but in temperate regions, especially in the fall and winter, the amount of sunlight received is limited. Other factors which limit the amount of ultraviolet rays received are:

1. The amount of clothing worn.
2. Tall city buildings.
3. Window glass panes.
4. Height of sun above horizon, e.g. depth of atmosphere.

Vitamin D Breast milk is a poor source of vitamin D and cow's milk contains only five to forty international units per quart. The diet of infants is therefore lacking in vitamin D unless the latter is added.

Of the many sterol derivatives containing the anti-rachitic factor, only two are of any practical importance. They are irradiated 7-dehydro-cholesterol found in animals, and irradiated ergosterol, vitamin D_2, which is of plant origin.

Contributory factors If a child receives a sufficient quantity of ultraviolet light or vitamin D, rickets will not develop, but in certain cases receiving minimum amounts of vitamin D, other factors come into play which increase requirements and so determine the degree of rickets. These are:

1. *Rapid Growth of Bone*: Rickets affects chiefly the growing ends of bones and it follows that the more rapid the growth of bone the more severe the lesion. Premature infants, because of their rapid growth and diminished mineral stores are more susceptible to the rachitic process.

Of less importance are:

2. *Quantity of calcium and phosphorus in the diet*: Low quantities will create a tendency to rickets.

3. *General metabolic disturbances*: Acidosis will cause decalcification of bones.

Incidence

Prior to the discovery of vitamin D in 1922, histological evidence of rickets

was found at autopsy in nearly all city children dying between four and eighteen months.

Between 1927–37, Park and Jackson showed a considerable reduction in the incidence of rickets. Most Canadian clinics report that rickets is seldom seen today. However, in 1953, at the Hospital for Sick Children, Toronto, sixteen new cases of simple rickets were diagnosed and treated. Vitamin D Resistant Rickets is, of course, much less common, but in large centers two or three cases are found each year.

Age Various forms and degrees of rickets are encountered in different age groups. Congenital rickets is rare and is attributed to maternal malnutrition. Terrafranca and Zeles report a case of congenital rickets, in which radiological evidence was found in a child three days old.

Follis, Park and Jackson report that rickets may begin to manifest itself at two weeks. Seldom, however, is a case seen before two months. A peak incidence is found at six months and then decreases, so that at the end of the second year the overall incidence is very low. At two years of age, children receive a mixed diet, spend more time outdoors and so are less susceptible.

Race Negroes are more susceptible to rickets than whites. Whether this is due to the deeper pigmentation of their skin or their lower socio-economic status is yet to be determined.

Geographic factors Rickets is found most often in temperate regions especially in the fall, winter and spring.

Pathology

The microscopic picture is that of osteoid tissue formation without calcification. The normal sequence of events in endochondral bone formation is disturbed.

Calcification of cartilage almost ceases at the epiphyseal discs and the mature cartilage cells continue to live causing marked thickening of the discs. Since the process is not entirely arrested, but continues in a few sites, the width of the discs is irregular. The cartilage cells do not arrange themselves in rows and invasion by the marrow vessels occurs in an irregular manner. The "rachitic' 'metaphysis develops between the cartilage and shaft, and consists of mature, proliferating cartilage, blood vessels, fibroblasts, osteoblasts and chondroosteoid trabeculae. This osteoid tissue fails to become mineralized and this zone is soft, easily bent and tends to bulge laterally. It is responsible for the thickening of the ankles and wrists, the *rachitic rosary* and the resulting deformities if allowed to progress. In rickets, not only are the epiphyseal-metaphyseal portions of the skeleton affected, but other parts as well. The bosses on the skull and new periosteal and endosteal bone are composed of osteoid tissue.

With healing, calcification takes place at the zone of preparatory calcification, cartilage cells begin to degenerate at the diaphyseal side of the discs and capillary penetration of the resulting spaces is resumed. There is active calcification of the osteoid tisue so that normal bone is formed.

Chemical Changes and Pathogenesis

Although some authors believe vitamin D has a specific action on bone formation, others believe that the underlying cause is diminished amounts of bone-forming minerals in the extracellular fluids. There may be a diminution in the serum calcium and phosphorus of both. In rickets uncomplicated by tetany, the serum phosphorus is diminished to 2 mg.% or lower (normal 4.5-7.5 mg.%) while the serum calcium may be normal or low. There is diminished absorption

of calcium and phosphorus from the intestine and interference with the normal renal tubular reabsorption of phosphates. The vitamin D content of the blood, as shown by Hess and Warkany, is reduced in active rickets. Its administration corrects the faulty calcium and phosphorus metabolism.

The serum alkaline phosphatase is elevated to above 20 King-Armstrong units in active rickets. This is of great diagnostic value.

It has recently been shown that there is constantly an aminoaciduria in all patients with simple rickets. This is also corrected by vitamin D, suggesting actions of vitamin D other than on bone.

Clinical Picture

The full-blown clinical picture of rickets is easily recognized, but the early cases may escape recognition. Early diagnosis and treatment are necessary to prevent the disturbances of growth and the development of deformities. The earliest signs may be craniotabes, beginning enlargement of the costochondral junctions and a slight thickening of the ankles and wrists. If rickets is suspected, the diagnosis can usually be established by radiological examination.

Advanced rickets is seldom seen nowadays because of early diagnosis and treatment. Briefly, its manifestations are as follows.

Head Evidence of craniotabes — a softening of the skull which permits it to be indented. Craniotabes is also seen in normal newborns (especially prematures), hydrocephalus and osteogenesis imperfecta.

There may be marked bossing of the skull, which if separated by deep sutures gives the typical "hot cross-bun" appearance. There may be late closure of the fontanelles.

Chest The ribs are beaded and these form the so-called *rachitic rosary.* This consists of large nodules at the costochondral junction and should be distinguished from the angular beading of scurvy. The sides of the chest become flattened, the sternum is displaced anteriorly, causing the pigeon breast deformity. About the costal insertions of the diaphragm, Harrison's sulcus may develop. There may be marked thoracic deformities which limit expansion.

Spinal Column This may be normal or there may be some kyphosis or lordosis.

Pelvis There may be a forward projection of the promontory of the sacrum, which if permanent, may later be a cause of dystocia.

Extremities There is the rachitic enlargement of the wrists and ankles. These cannot be visualized on X-ray examination. There may be bowing of the legs, sabre shin, knock-knee, coxa vara and pathological fractures.

Ligaments The ligaments, especially of the larger joints, become quite lax.

Muscles These are small, flabby and lacking in tone. Laxity of the abdominal wall muscles may cause the characteristic pot-belly.

Complications

Simple rickets may be complicated by tetany. The serum calcium is not characteristically low in simple rickets probably due to compensatory hyperactivity of the parathyroid glands. However, sometimes a normal serum calcium is not maintained and occasionally it may fall below 7-7.5 mg.% causing latent or manifest tetany. Indeed, it may be the presenting sign. This may be attributed to failure of parathyroid compensation or may be associated with the therapeutic administration of vitamin D which produces a too rapid transit of calcium into the bones. Tetany occurs most often in children between four months and

three years of age, and is more common in males than in females.

Respiratory infections, especially bronchitis and bronchopneumonia, are common.

There may be gastrointestinal disturbances such as diarrhoea and constipation, loss of weight, iron-deficiency anaemia, lymphadenopathy and splenomegaly.

Differential Diagnosis

The following conditions should be considered in the differential diagnosis.

1. Vitamin D resistant rickets.
2. Osteogenesis imperfecta.
3. Scurvy.
4. Achondroplasia (Chondrodystrophy).
5. Congenital deformities of the chest.
6. Other causes of tetany in patients presenting with this symptom-complex.
7. Hydrocephalus.

Diagnosis

The diagnosis is made on:

1. The history.
2. Physical examination.
3. Blood chemistry.
4. Radiological examination.

The first three have already been discussed. The radiological examination is done on areas of active growth, usually the wrists and knees. In active rickets the changes in the wrists are as follows (see Fig. 1):

1. The distal ends of the radius and ulna are cupped and frayed.
2. The distance between secondary centres of ossification, if present, and the distal ends of the radius and ulna is increased.
3. Decreased density of the shaft.
4. Coarsening of trabeculae.

With healing, there is the appearance of the line of preparatory calcification which is separated from the shaft by an area of decreased calcification. Later, the osteoid becomes calcified and the shaft seems to "grow" toward the line of preparatory calcification. This line is always concave and is characteristic of healing rickets (see Fig. 2).

Prognosis

This depends on the degree of the rachitic process and the adequacy of

Figure 1

Figure 2

treatment. Healing begins in a few days, and progresses until bone structure is returned to normal. The correction of deformities may take a long time and may be impossible.

Prevention

Rickets can be prevented by sufficient exposure to sunlight or by the oral administration of vitamin D. Simple rickets is a preventible disease and the cases of rickets that are seen in large cities today are the result of ignorance or neglect. It is the duty of every medical practitioner to *eliminate* this disease.

For prophylaxis 800 I.U. of vitamin D are administered to infants from the tenth day of life. This is provided by five drops of oleum percomorphum daily or one teaspoonful of cod liver oil. Premature infants and twins of low birthweight require about 2000-3000 I.U. of vitamin D per day, in addition to a diet with a high mineral content. It should be remembered that individual requirements for vitamin D are quite variable.

Treatment

This consists of the administration of 2000 to 3000 I.U. of vitamin D daily for one month in the form of about fifteen drops of oleum percomorphum. If serum calcium is low, ten grains of calcium lactate t.i.d. should be started before vitamin D therapy is instituted. These doses produce radiological evidence of healing within two to four weeks, except in the cases of Vitamin D Resistant Rickets for which massive doses are required.

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ADRENAL INSUFFICIENCY IN CHILDREN

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ABOUT 100 years ago, 1855, Thomas Addison gave the first accurate clinical and pathological description of a disease of the "Supra Renal Capsules" which bears his name. Subsequent work has increased our knowledge, especially as regard to the physiological and biochemical changes which are associated with this condition.

To-day we recognize three main functions of the supra-renal cortex:

1. A factor regulating the salt and water concentration in the body.
2. A factor which plays a part in carbohydrate regulation and is frequently referred to as the S. or sugar factor.
3. A factor which influences nitrogen metabolism and is closely associated with the production of the secondary sex characteristics, sometimes referred to as the N. hormone of the supra-renal cortex.

It has not been possible for the anatomists and histologists to definitely ascribe a particular function to a particular area of the cortex, though it has been suggested that:

(a) the zona glomerulosa is associated with the production of the salt and water regulating hormone.

(b) the middle layer or zona fasciculata is responsible for the elaboration of the sugar regulating hormone.

(c) the inner layer, the zona reticularis elaborates the nitrogen regulating hormone which is also responsible for producing many of the secondary sex characteristics.

Others have suggested that an excess or alteration in one type of hormone may interfere with the function of the others.

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It must be remembered that there is in the foetus and in the newborn infant a disproportionate enlargement of the adrenal cortex due largely to a foetal cell layer which later atrophies and disappears. The function of this foetal layer of cells is not understood but may be necessary to protect the infant from the large amounts of various maternal hormones circulating in the blood during pregnancy.

Addison's Disease represents a loss of all three functions of the adrenal cortex and is associated histologically with complete destruction or disappearance of the normal architecture of the gland.

More recent work has shown that it is possible for the supra-renal glands to be deficient in only one type of hormonal effect whilst the others are apparently normal. In other instances, a deficiency in one type of hormonal effect may be associated with an over-activity of one of the other groups.

Classification

In order that we may understand the problem more clearly a classification of adrenal insufficiency has been drawn up; partly on a histological and partly on a functional basis.

COMPOSITE OR COMPLETE FAILURE

1. aplasia
2. hypoplasia
3. atrophy
   - (a) primary
   - (b) secondary to pituitary insufficiency
     - (i) pituitary disease
     - (ii) removal of adrenal tumor
     - (iii) withdrawal of cortisone therapy

4. destruction of glands
   (a) infection, e.g. tuberculosis
   (b) haemorrhage
      (i) trauma
      (ii) haemorrhagic disease
      (iii) infection (meningococcemia)
5. surgical removal

PARTIAL ADRENAL CORTICAL INSUFFICIENCY

1. deficit in salt and water regulating effect.
2. deficit in sugar regulating hormone.
3. deficit in nitrogen (androgenic) hormones.

One function only may be deficient while the others may be normal or overactive. Occasionally, two functions may be deficient.

The composite type of chronic adrenal insufficiency is the one commonly seen in adult life but is rarely seen in infancy. On the other hand, the acute form of composite adrenal insufficiency is seen more commonly in infancy.

Complete Failure

APLASIA has been encountered rarely—usually associated with anencephalic monster or other anomaly incompatible with an extra-uterine existence.

HYPOPLASIA likewise is generally observed only on postmortem. Four cases—all male—have been reported by our pathological department in the last two years. One had congenital heart disease; one had co-arctation of the aorta; one had multiple congenital defects; and one had cirrhosis of the liver. They all died within a few weeks of birth. In only one were electrolyte studies carried out. The values were within the normal ranges. What part the hypoplastic adrenals played in the deaths of these infants is uncertain—that they were a contributing factor seems likely.

ATROPHY

Primary Atrophy of the adrenal in a child was first reported by Snelling and Erb from the Hospital for Sick Children in Toronto. This occurred in a 9½ year old boy who had all the typical symptoms of Addison's Disease—asthenia, pigmentation, hypotension and electrolyte depletion. He died in the days when adequate therapy was not available.

Secondary to Pituitary Insufficiency

(i) *Pituitary Disease* Several cases of craniopharyngioma have been encountered, who suffered from adrenal insufficiency and whose operative and postoperative care was greatly improved by the exhibition of adrenal cortical hormones.

Presumably other destructive lesions of the pituitary might also lead to inadequate adrenal stimulation.

(ii) *Removal of Unilateral Adrenal Tumour*

This has been reported as a cause for sudden collapse due to adrenal insufficiency. The contra-lateral adrenal is atrophic since the excess production of adrenal hormone by the tumor has suppressed the normal ACTH mechanism of the pituitary.

In one recent case of carcinoma of the left adrenal, pre-operative administration of Cortisone and post-operative administration of ACTH and Cortisone led to a rapid uneventful recovery.

(iii) *Withdrawal of Cortisone Therapy*

Prolonged use of large doses of cortisone causes suppression of pituitary ACTH function. Stressful situations occurring at varying times following its withdrawal have been reported as causing acute signs of insufficiency (Sprague, Mayo Clinic).

DESTRUCTION OF THE GLANDS

Infection Tuberculosis has been recognized, since Addison first described

the condition, to be one of the chief factors in destroying the adrenal glands. It was the only recognized cause of adrenal insufficiency in children, until Snelling's case in 1935 and the recognition of partial and mixed syndromes by Butler, Ross & Talbot in 1939.

Haemorrhage (i) *trauma and*
(ii) *haemorrhagic disease.*

Snelling & Erb reporting from our hospital in 1935 (Jour. Paed. 6: 22, 1935) found supra-renal haemorrhages 43 times in 3,637 consecutive autopsies—an incidence of 1.2%. Fifteen occurred in newborn infants. In ten of these, both adrenals were apparently destroyed.

This condition is rarely recognized ante-mortem. The signs of listlessness, vomiting, pallor, dehydration and shock usually are attributed to a difficult delivery, cerebral birth injury or sepsis. If one searches for it, a mass may be felt in the flanks; some cases present with twitching, convulsions and fever.

We have recently had a six year old girl in hospital who has had hypoglycemic convulsions on two occasions; one in infancy and one recently. X-rays reveal evidence of calcification in both adrenals. Her tuberculin test and chest X-ray are negative. All functional tests for adrenal and pituitary function are within normal limits. One strongly suspects, however, that this child has had haemorrhages into her adrenals—possibly

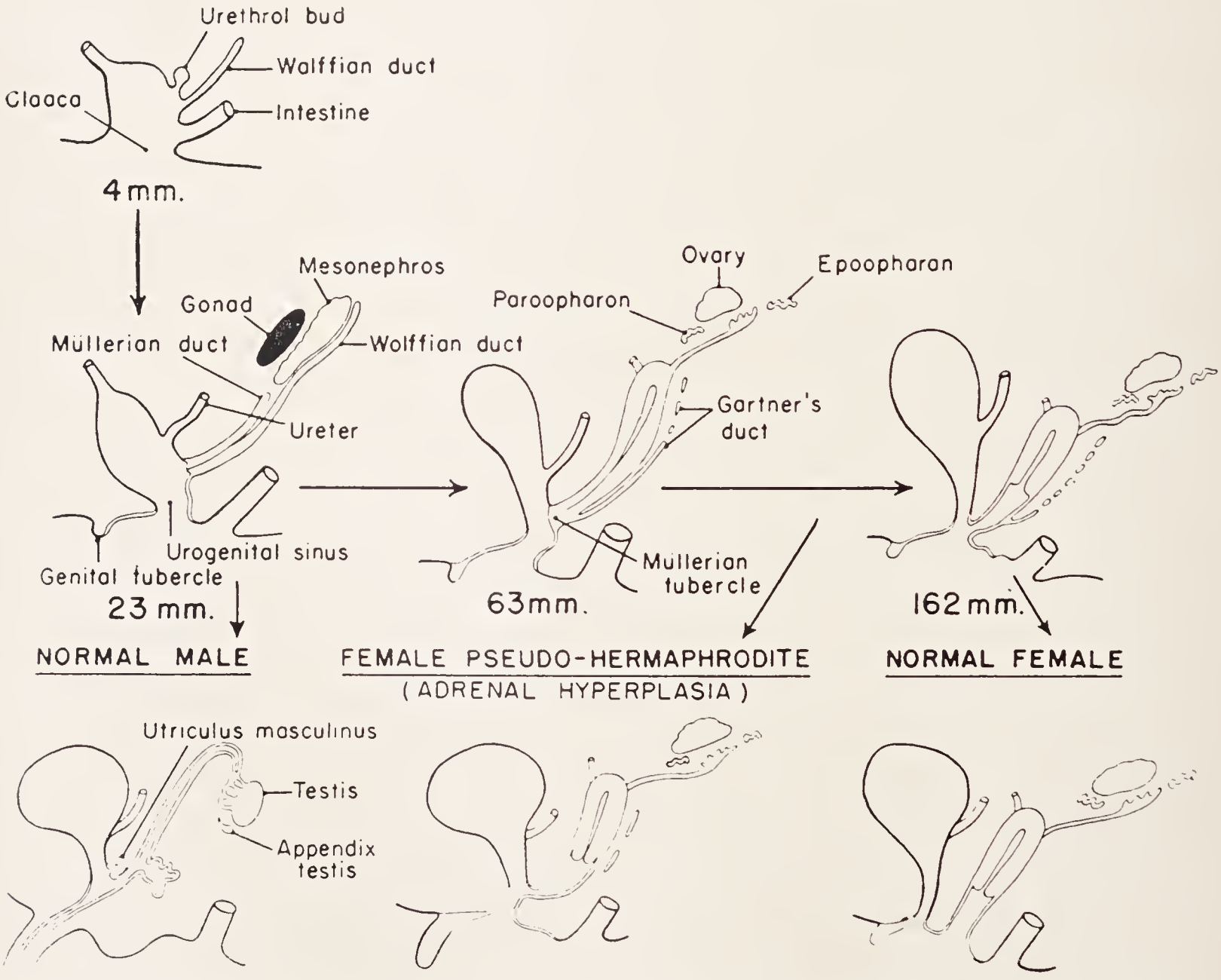

Fig. 1.—Embryology of Human Genito-Urinary System from L. Wilkins; Pediatrics 3; 533, 1949.

at birth—and that she has a greatly reduced adrenal cortical reserve—though no signs of insufficiency, other than the two bouts of hypoglycaemia, can be demonstrated.

The cause of neonatal haemorrhage into the adrenal glands is obscure. Perhaps the increased vascularity coupled with mild trauma—e.g. breech delivery or haemorrhagic disease may explain some cases.

(iii) *Infection*:—Waterhouse Friedricksen Syndrome—The most fulminating cases of adrenal insufficiency are those associated with meningococcal infections. Death may supervene within a matter of hours of the onset of the illness by virtue of complete haemorrhagic destruction of the adrenal glands.

In all cases the severe meningococcaemia adrenal cortical hormone therapy is indicated.

SURGICAL REMOVAL

Since replacement therapy has become available, surgical removal of both adrenal glands, where indicated, has been made possible. We have performed bilateral subtotal adrenalectomy on one child with severe Cushing's Disease due to bilateral hyperplasia. He is well and free of symptoms on maintenance therapy two years following his operation.

Partial Insufficiency

One of the most interesting chapters in clinical endocrinology has been the discovery of the partial and mixed types of adrenal insufficiency in infancy.

Although the composite type of adrenal cortical failure in the infant is usually fulminating in character, partial adrenal cortical failure usually presents a subacute picture.

In the majority of instances the infant appears well at birth and may appear so for several ways or weeks. However, the weight loss is excessive and if the nurse in charge is astute she will have been impressed with the excessively large amounts of urine passed. At any time the dehydration caused by renal losses may be aggravated by the onset of vomiting and diarrohea, leading rapidly to a state of circulatory collapse and shock.

Fig. 2.—Female Pseudohermaphrodite showing enlarged clitoris, large wrinkled labia and single opening of urogenital sinus.

In many cases the vomiting is projectile and has been mistakenly ascribed to pyloric stenosis or intestinal obstruction. Frequently a laparotomy has been performed to the detriment of the patient. In not a few cases, the patient is assumed to be suffering from an infection and therapy is directed only towards this end. Some cases may indeed have a concomitant infection but unless the underlying adrenal disease is treated as well, the infant's progress leads to a rapidly fatal termination.

While a few infants present with the signs and symptoms of deficient salt

regulating hormone only, it is much more common for deficiency of this hormone to be associated with an over-activity of the nitrogen or androgenic hormone. Thus the male infants may have over-developed genitals (macro-genito-somia praecox).

The females (pseudohermaphrodites) have an enlarged clitoris, large wrinkled scrotal like labia and a urogenital sinus instead of separate urethral and vaginal openings. (Fig. 2)

The female cases are frequently thought to be males with hypospadias. It is, however, easy to establish the true sex by means of a skin biopsy as the female sex chromatin can be readily distinguished in the cells of all tissues.

The condition is best illustrated by an example:

L.K. born June 21st, 1948.

This patient was referred by the outside physician to the surgical clinic for repair of a hypospadias at four weeks of age. As the child was obviously ill it was referred to medicine. There was a history of more or less vomiting from birth, the stools were 3–4 per day, slightly loose. The baby was drowsy, did not feed well and was losing weight.

Physical examination revealed a rather markedly dehydrated infant which was in all likelihood a female pseudohermaphrodite, rather than a male with hypospadias.

Electrolytes—*Na 120; K 7.9; cL 100 meq/L 17 keto. 8.5 mg/24 hrs.* Responded to 1 gram salt orally, 5 cc. cortical extract q.4.h. × 6 and blood transfusion. Was sent out on a one-gram salt diet—was back in three weeks time with a temperature of 102; shocked and dehydrated. Na 138; cL 103; K. 8.2. Did well on 2 grams salt and 0.5 mg. D.O.C.A. daily. Two pellets (75 mg. each) D.O.C.A. implanted; sent home on salt as above. She did well for nine months. Developed nasopharyngitis, became exceedingly listless, anorexic and moderate fever. Na 151; K 6.0; cL 80. Normal glucose tolerance curve. Two more pellets (75 mg. each) D.O.C.A. inserted. Laparotomy revealed normal female genitalia (section of skin also confirmed the sex).

The hypertrophied clitoris was removed. The child is now 6½ years old; has had no further therapy and takes no extra salt. She is tall for her age and her bony maturation is that of a 13 year old. She has rather marked pigmentation. Her electrolyte picture and her glucose tolerance tests are normal. She has received no cortisone therapy.

In the past six years at the Hospital for Sick Children, we have recognized 7 cases of adrenal insufficiency of this type, 4 cases in girls and 3 cases in boys. All the girls were pseudohermaphrodites. All the boys have shown at birth or developed subsequently macrogenito-somia praecox.

One female and one male are dead.

Of the living, all those over 18 months (3 cases) no longer require either salt or D.O.C.A. All but the first case mentioned are receiving suppressive Cortisone therapy.

Wilkins (J. Paed. 41: 860, 1952) reports that there has been a synergistic action between D.O.C.A. and Cortisone in his cases. The dose of D.O.C.A. has been less when Cortisone is employed concurrently.

The second type of partial adrenal cortical deficiency is concerned with a lack of the S or sugar regulating hormone. The first case of this type was described by Geppart et al. in 1950. (J. Paed. 37; 1; 1950). There was also some evidence of deficiency in the salt and water hormone but there were no signs of inter-sexuality as noted above. The terminal illness in this case was ushered in with diarrhoea and fever. These led to convulsions which were associated with very low blood sugar values, a reduction in Na and Cl and elevation in K values. Adrenal cortical extract intravenously, salt and sugar solutions plus D.O.C.A. while effective on a number of occasions, were ineffectual in restoring sugar and electrolyte in his final illness. At the time of death, his blood sugar was 30 mg.% Autopsy revealed a hypoplasia of both adrenals; microscopically there was complete ab-

sence of the zona fasciculata and some scattered remnants of the zona glomerulosa, which were thought to be responsible for preventing excessive electrolyte disturbance.

Recently McQuarrie (Am. J. Dis. Child. 87: 399, 1954) has reported 25 cases of idiopathic hypoglycemia. In none of these was he able to demonstrate any evidence of adrenal insufficiency by such means as the Adrenaline or Thorn Test, or by alterations in the 17 ketosteroids or 11 oxysteroids. However, in all cases in which it was tried, prolonged use of ACTH controlled the hypoglycemia and after a period of months or years, discontinuance of the drug was not followed by the return of symptoms.

In view of the fact that no evidence for hyperinsulinism, liver disease, pituitary or adrenal disease, or other factors responsible for the low blood sugar were found, he indicated that the cause was still unknown. With this one must agree but one cannot help but note that there is apparently a functional adrenal insufficiency—which may be due to inadequate amounts of S hormone production—a condition corrected by ACTH or an excessive need for 11-oxysteroids. The latter is suggested by McQuarrie's finding that large doses of the latter drug was necessary to counteract the hypoglycemia.

Another piece of circumstantial evidence lies in the fact that just as the patients with loss of salt and water hormone occur in infancy so do many of these cases; also like them, after a period of supportive therapy, the condition appears to right itself. It has already been shown that the adrenal cortex undergoes a marked change following birth—a change which might interfere with the normal functioning of the gland during early infancy but may correct itself later. One further piece of circumstantial evidence is that like insufficiency of the salt hormone, this condition has a strong familial incidence. The difficulty in detecting reduced values of 11 oxysteroids which at this age are normally only about 0.1 mg/ day are very great, and unless biological assay rather than chemical assays of this fraction are carried out, one cannot be sure of the functional integrity of this mechanism. No other test can be considered really specific.

While in no sense proved, some of these cases might be regarded at least as functional adrenal insufficiency of the S-hormone. That these are a very serious and practical problem is borne out by McQuarrie's study, which indicates a serious degree of cerebral damage from repeated or constant hypoglycemia. We have had 3 similar cases—a short history of one wil serve to illustrate the problem.

R.H.—A 9-month baby was admitted in 1947 with a story of having been normal until about 4 months of age, when she began to have vacant or staring spells—suggestive of petit mal. These were followed in a few weeks by frank convulsions which caused her to be admitted to hospital. E.E.G. showed diffuse changes. A.E.G. showed cortical atrophy. However, a fasting blood sugar showed a value of only 25 mg.% (true blood sugar). A glucose tolerance test showed a fasting of 25 mg.% rising to 90 and falling to 20 mg.% in 2 hours. Adrenaline caused a normal glycaemic response to 160 mg.% but with a rapid fall to low fasting levels.

Blood insulin determinations in the Banting Institute revealed normal levels. Nevertheless, because of the seriousness of the symptoms, a laparotomy was performed and 65% of the pancreas was removed. Neither assay, nor histological examination revealed evidence of excessive insulin. The symptoms promptly returned and at a subsequent operation a subtotal pancreatectomy left a portion of pancreas less than the size of a peanut. Again, no evidence for increased insulin production by this portion of the gland could be demonstrated.

However, the child was completely relieved of her symptoms and has a normal glucose tolerance curve even 6 years afterwards. She is, however, still quite retarded mentally. Such cases to-day are best treated with long-acting ACTH.

Deficit of the androgenic or N hormone of the adrenal as the only deficit in adrenal function has not been described in infancy or elsewhere to the writer's knowledge. It would seem reasonable to expect it and probably with increased knowledge and more careful examination such conditions may come to light.

Treatment

acute composite adrenal insufficiency

In cases of acute adrenal insufficiency in infancy, it is our practice to:

1. Give 15-25 cc. of A.C.E. intravenously stat; and 10-20 cc. IM. q.4.h. until the immediate danger is passed.

2. An intravenous of 5% glucose in normal saline is started immediately 75-100 cc/lb/24 hours.

3. Cortisone 100-200. mg. I.M. stat and 25 mg. repeated daily. If the child is not vomiting and can swallow, Cortisone 25 mg. t.i.d. may be given orally instead.

When hydrocortone becomes available, it should be given I.V. 25-50 mg. If symptoms are prolonged, D.O.C.A. may be employed as outlined below.

partial adrenal insufficiency (Subacute)

(a) Associated with excess androgen production.

1. 2-3 Gm. salt per os—daily.
Supplement by saline interstitials if hydration difficult.
2. Administer D.O.C.A. in oil – daily starting with 0.1 cc = 0.5 mg. D.O.C.A. Increase q. 2 days until electrolyte balance is restored and maintained without evidence of hypertension or oedema.
3. Now insert D.O.C.A. pellets 75 mg. size—approximately one for each 0.5 mg. D.O.C.A. required.
4. If edema or blood pressure rises after three, reduce salt to re-establish equilibrium. If electrolytes fall, increase salt by 1-2 Gm. In some cases a further pellet or two may have to be added.
5. If ketosteroids are high and masculinization is prominent, 15-20 mg. Cortisone I.M. q. 2 days may suppress overactive adrenal by depressing ACTH activity. Most children prefer to take 50-75 mg. a day per os.

In cases of idiopathic hypoglycaemia, 10-15 mg. ACTH daily or 50 mg. Cortisone daily may be employed.
If long-acting ACTH, 15 mg. q. 2 days may be adequate.

Prognosis

In partial adrenal insufficiency treatment has to be continued for 1-2 years at which time many appear to have obtained a reasonable degree of function of their own. There have been reports of a few who have required prolonged therapy.

It would appear the part of wisdom to give these children replacement therapy for acute stressing situations.

In conclusion, one may say that from pathological studies and more adequate biochemical analyses we are beginning to recognize adrenal insufficiency as an important and not uncomon complication in the newborn state as well as in the older infant and child.

CYANOSIS IN THE NEWBORN

MISS D. W. JOHNSON, 5T5

CYANOSIS is frequently seen in the newborn period: its presence usually signifies anoxia. Clifford states that anoxic damage is the primary cause of 60% of neonatal deaths and at least as high morbidity.[3] As the duration of anoxia which the newborn can endure without irreversible injury and death is short, it is important to ascertain the cause of the cyanosis and to initiate treatment as soon as possible. The physiology, aetiology, differential diagnosis, investigation, and emergency treatment of the more common causes of neonatal cyanosis will be discussed. In this paper, emphasis will be placed on the purely respiratory causes.

Physiology

Cyanosis may be defined as the diffuse dusky or bluish colour imparted to the skin by the presence of 5 Gm. or more of reduced haemoglobin per 100 cc. of peripheral blood (subpapillary venous plexuses). Since the amount of unsaturated haemoglobin is a simple fraction of the total haemoglobin present, it is clear that the more concentrated the haemoglobin, the more readily will the patient become cyanosed. Newborn infants, with a normal haemoglobin of 18 Gm.% are therefore predisposed to cyanosis, which thus becomes an *early* sign of anoxia. For example, a newborn will become cyanotic when slightly more than one-quarter of his total haemoglobin is in the reduced form, whereas a three months old child with a normal haemoglobin of 11.4 Gm.%, will not become cyanosed until almost one-half of his total haemoglobin is in the reduced form.

Anoxia has been classified into four types by Barcroft, Peters and Van Slyke: *Anoxic anoxia* or anoxaemia is a deficit in the tension at which oxygen is delivered to the tissues. Foetal blood may be poorly oxygenated due to maternal respiratory or heart disease or excessive anaesthetic. Neonatal pathology in the respiratory system will also prevent adequate oxygenation.

Anaemic anoxia occurs as a result of insufficient circulating haemoglobin, either by haemolysis (Rh incompatibility) by haemorrhage or by the alteration of the haemoglobin to a stable compound which is unable to take up oxygen. (Sulph-haemoglobinaemia and methaemoglobinaemia).

Stagnant anoxia is a problem of impaired transport of well oxygenated blood through a local area (constriction of a limb by the cord) or sometimes as a general stagnation (neonatal shock or heart failure).

Histotoxic anoxia results from the inability of the tissues to utilize adequate amounts of oxygen, usually due to direct poisoning. The extent to which barbiturates and certain anaesthetics cause this form of anoxia as opposed to depression of the respiratory centre has never been accurately determined.

Development of the Respiratory System

embryology

The development of the respiratory tree takes place in two stages. The first consists of the elaboration of a system of branching tubules during the initial 20 weeks of intra-uterine life. They arise from a bud on the primitive endodermal

tube and are separated widely by a core of mesenchymal tissue. The second stage continues until after birth and consists of the vascularization of the new tubular frame work associated with progressive reduction of the intervening mesenchyme. By the 28th week of gestation, enough capillaries are exposed to tubular lumens to allow oxygenation sufficient to sustain life. Each succeeding week serves to increase this exposed vascular bed, (and thus the oxygenating capacity), until, at term, normal pulmonary function is accomplished with comparative ease.

RESPIRATION BEFORE BIRTH

It has been established that fluid is always present in the developing fetal lung, but the nature of this fluid, whether transudate or inhaled amniotic fluid, has been a matter of debate. Windle and his workers maintain that inspiration of amniotic fluid occurs only when the respiratory centre is stimulated by anoxia. Recently, however, Davis and Potter have been able to show that respiratory activity begins early in fetal life. They selected cases requiring subsequent therapeutic abortion, introduced thorotrast into the amniotic sac and later examined the lungs for the dye. If the lungs are filled with amniotic fluid at birth, one might wonder how the alveolar exchange of gas is initiated in the newborn. It must be remembered that intra-uterine respirations are very shallow, that the area occupied by the fluid is only a small fraction of the potential air space, and that the fluid can be rapidly absorbed. Even increased amounts of fluid, aspirated due to abnormal stimulation of respiratory activity can be absorbed; however, the excessive movement of the anoxic fetus may increase the amount of desquamated particulate matter in this amniotic fluid.

RESPIRATION AFTER BIRTH

Extra-uterine respiration is a continuation of intra-uterine respiration, and any infant whose central nervous system has not been depressed before birth and whose respiratory tract is intact will breathe spontaneously immediately after delivery.

The initial effort required to expand the alveoli from their fetal state is greater than that required to maintain a tidal flow of air in the once expended lung. The cohesion of moist surfaces must be overcome and this requires a relatively high negative pressure. According to Smith[5] an intrapleural negative pressure of 25-30 cm. of water is necessary for primary separation, while 10-15 cm. pressure is sufficient thereafter.

In order to overcome this initial resistance and maintain respiration the following conditions must be fulfilled:

1. maturity of the lungs
2. intact C.N.S.
3. patent air passages
4. alveoli which are capable of expansion
5. a thoracic cage sufficiently rigid to permit a negative pressure to develop
6. diaphragms which are capable of moving downwards

Differential Diagnosis

The causes of cyanosis in the newborn and neonatal period may be classified as follows:

I RESPIRATORY

- A. Antepartum
  1. Interference with oxygenation of fetal blood by placenta
  2. Interruption of circulation between placenta and fetus
- B. Partum
  1. Prematurity
  2. Maternal analgesia and anaesthesia

3. Birth trauma
4. Bronchial obstruction
5. Pneumonia

C. Postpartum
1. Secondary atelectasis
   (a) internal obstruction
   (b) external compression
2. Inadequate alveolar exchange
   (a) Pneumonia
   (b) Hyaline membrane disease
   (c) Pneumothorax and pneumomediastinum
3. Pulmonary haemorrhage
4. Congenital Anomalies
   (a) Agenesis of the lung
   (b) Tracheal stenosis
   (c) Tracheo-oesophageal fistula
   (d) Diaphragmatic hernia

II INFECTIOUS
A. Local
B. General

III CENTRAL NERVOUS SYSTEM
A. Direct
B. Indirect

IV CIRCULATORY
A. Congenital Heart Disease
B. Altered Haemoglobin

V METABOLIC
Tetany of the Newborn

RESPIRATORY

Antepartum Anoxia

1. Interference with oxygenation of fetal blood by placenta

(a) Separation of villi from maternal blood as in abruptio placenta and some cases of placenta praevia.

(b) Lack of oxygen in maternal blood as seen in maternal pulmonary or circulatory disease, or in excessive use of anaesthetics or analgesics. The latter has been the subject of much debate and is difficult to assess. There is no evidence that analgesic drugs in therapeutic doses interfere with fetal circulation, but large doses, especially if administered late in labour, may cause depression of the respiratory centre, so that anoxia becomes apparent after the cord is clamped. Anaesthetics are dangerous because most of them require a marked reduction of oxygen in the maternal blood.

(c) Maternal blood does not circulate effectively as in maternal shock, eclampsia or rupture of the uterus.

2. Interruption of circulation between fetus and placenta

This is seen in prolapse, knots, entanglements, excessive twisting or stretching of the umbilical cord. When the heart sounds disappear and fetal circulation ceases during labour without apparent reason it is usually due to the cord. Severe compression of the chest may interfere with the venous return from the head and cause cyanosis of the head and neck, which may persist for days and is known as traumatic cyanosis.

Partum Anoxia

Apnoea neonatorum is defined as a disturbance of the respiratory mechanism developing during or shortly after birth and characterized by absence or irregularity of respiratory movements and cyanosis. It has been classified by Flagg into three stages:

Depression A mild degree of anoxia with a tendency to duskiness or recurrent cyanosis, good muscle tone and resistance, free but slow and irregular respirations, and slow but vigorous heart beat.

Spasticity A moderate degree of anoxia with marked cyanosis of mucous membranes, blotching of the skin and general pallor, diminished muscle tone, no resistance, irregular gasping respirations and heart seunds of poor quality which may be slow or rapid.

Flaccidity A severe degree of anoxia with pallor or grey cyanosis, no muscle

tone, no resistance, no crying, occasional or absent breath sounds, and only an occasional flicker of the heart.

Failure to establish normal respirations may be due to intra-uterine anoxia which has depressed the respiratory centre, thus initiating a vicious cycle; it may be due to factors related to the actual birth; or it may be due to the inability of the foetus to change suddenly to pulmonary oxygenation.

1. Prematurity

By far the most common cause of death in premature infants is immaturity of the lungs. As discussed previously the lungs can absorb enough oxygen to support life by the twenty-eighth week of gestation and their efficacy increases with each succeeding week. However, the less mature they are, the less the pulmonary reserve the infant possesses to overcome any other factors which may interfere with pulmonary function. The premature infant is also more likely to have a poorly developed thorax and musculature, so that it is difficult to develop sufficient negative pressure to establish respiration. Premature infants are also more susceptible to hyaline membrane disease and to pneumonia which will be discussed later. Another frequent cause of death in the premature infant is intracranial or pulmonary haemorrhage. This is caused by a combination of immaturity of the blood vessels, anoxia, infection and haemorrhagic disease of the newborn.

2. Maternal analgesia and anaesthesia

Apnoea due to these factors, which has been discussed previously, usually wears off quickly. If due to pentothal the infant develops a characteristic purple colour. Stimulation and an adequate supply of oxygen should be given until narcosis has been dissipated.

3. Birth trauma

(a) Phrenic nerve paralysis causing immobility of the diaphragm and limiting the space for lung expansion is usually associated with a brachial palsy. Cyanosis develops and an irregular, laboured type of breathing which is completely thoracic, with no bulging of the abdomen. Breath sounds are diminished on the affected side. The diagnosis is confirmed by fluoroscopic examination.

(b) Intracranial haemorrhage may be traumatic when the head is large, labour prolonged or forceps are used injudiciously. It can occur in the subdural, subarachnoid, or ventricular spaces or within the brain substance, and is more common in the premature infant. The clinical manifestations are extremely variable in type, severity and time of appearance, but the diagnosis should always be considered when a baby has depressed respiration or attacks of cyanosis.

(c) Massive adrenal haemorrhage may result from trauma in a breech delivery. The infant usually dies shortly after birth in extreme shock with cyanosis and hyperthermia.

4. Bronchial Obstruction

Congenital atelectasis results from obstruction of the bronchial tree. It may be caused by aspiration of mucus, blood, meconium or debris or by complete atresia of the trachea or bronchi. Other causes of obstruction usually do not become apparent until later in the neonatal period.

5. Pneumonia

Pneumonia is often associated with early rupture of the membranes. Almost all pneumonias originating before birth are caused by aspiration of bacteria in the amniotic fluid, usually Staphylococci, Streptococci or Colon bacilli. Rarely

haematogenous pneumococcal infections occur.

Postpartum Anoxia

1. Secondary Atelectasis

Whenever the larynx, trachea or bronchi are completely obstructed the air in the lung distal to the obstruction is absorbed and atelectasis results. Secondary atelectasis is suspected when symptoms of dyspnoea, stridor and cyanosis develop with decreased breath sounds.

(a) Internal obstruction may be caused by:

(1) aspiration, especially in prematures whose cough reflex is poorly developed
(2) infections such as tuberculosis, retropharyngeal abscess or quinsy. These are rare in newborns
(3) stenosis due to scar tissue following traumatic intubation
(4) foreign bodies
(5) tumours

(b) External compression may be caused by:

(1) mediastinal tumours
(2) enlarged thyroid
(3) anomalous vessels as in a double aortic arch or aneurysm
(4) enlarged lymph nodes
(5) mediastinal emphysema
(6) birth trauma
(7) enlarged thymus—*very* rare

2. Inadequate Alveolar Exchange

Poor oxygenation in the lungs is responsible for respiratory failure in pneumonia, hyaline membrane disease, pneumothorax and secondary atelactasis. The latter has been discussed above.

(a) Pneumonia

Bronchial pneumonia that develops in the first 24 hours is usually intra-uterine in origin, and commonly follows a long second stage or a difficult delivery, where anoxia has caused increased respiratory efforts or there have been excessive bacteria in the foetal environment. The clinical diagnosis is often difficult. The temperature, breath sounds, and X-ray picture may appear normal, but the infant usually looks ill and a positive blood culture is often obtained. There may be hyperirritability, irregular twitching or actual convulsions, and cyanosis. In pneumonia resulting from intra-uterine infection the alveoli are filled with debris and leucocytes, but no fibrin.

Pneumonia in the infant over one week of age is the chief cause of death. It is still bronchial in type but may become confluent. Destruction of tissue is more common with the formation of abscesses, and fibrin is now found in the exudate. The severity of the pneumonia as shown by the outcome seems to bear little relationship to the pathological appearance.

Lipoid pneumonia may develop in small infants from the aspiration of milk or oily nose drops.

Pneumonia in the premature infant is very common and of a special type. The alveolar lumens are filled with leucocytes and lined by a single layer of cells that appear to be macrophages.

Virus pneumonitis has been described in epidemic and sporadic form. Clinically it is characterized by coughing, sneezing, dyspnoea, cyanosis and a variable elevation of temperature. Throat smears show cytoplasmic inclusion bodies and these are often present in the throat swab of the mother also. The infection involves the bronchial tree from larynx to alveoli and is presumed to be due to a virus although none has been isolated.

(b) Hyaline Membrane Disease

This condition is a distinct clinical and pathological entity but there is still dis-

agreement over its precise aetiology. It is more frequently seen in premature infants, infants of diabetic mothers, and in those delivered by a Caesarian section. They may breathe spontaneously at birth and appear normal for one to two hours. Then progressive cyanosis and dyspnoea with sternal retraction develop; death usually occurs in the first forty-eight hours from anoxia and exhaustion. On pathological examination the lungs are dark red and have the consistency of liver. Microscopically, most of the alveoli are collapsed and the inner surfaces of the ducts that remain open are lined by an irregular layer of homogeneous acidophilic material.

The cause of hyaline membrane formation with resorption atelectasis, is a matter of debate. Some workers feel that it is due to increased amounts of amniotic fluid and debris in the pulmonary alveoli; others believe that it is due to a transudate from immature or damaged capillaries; many believe that it is caused by a combination of these factors.

(c) Pneumothorax and Pneumomediastinum

Pneumothorax occurs in about one per cent of newborn infants. It may be spontaneous or traumatic, but is usually caused by the rupture of over-inflated alveoli. It is more frequently seen on the left side and may result from too vigorous attemps at resuscitation. Clinically this condition is characterized by the sudden onset of dyspnoea, cyanosis and shock. In pneumothorax the heart sounds are distant, the heart is displaced, the percussion note is resonant and the breath sounds are diminished or absent. In pneumomediastinum there is a bulging of the precordium, distended neck veins and low blood pressure. The diagnosis is confirmed by fluoroscopic examination.

3. Pulmonary Haemorrhage

Massive pulmonary haemorrhage accounts for some stillbirths and deaths due to respiratory difficulty in the first few days. It may be subpleural, intra-alveolar, interstitial or perivascular, and at times may involve all sites. Haemorrhage may be due to trauma, anoxia, haemorrhagic disease of the newborn or blood dyscrasias such as congenital hypoprothrombinaemia or fibrinopenia.

4. Congenital Anomalies

(a) Agenesis of the lung occurs about once in fifteen thousand births and if bilateral is incompatible with life.

(b) Tracheal stenosis is a rare congenital anomaly in which varying degrees of narowing occur, the trachea usually being involved in its entirety.

(c) Tracheo-oesophageal fistula occurs as several types but the commonest consists of an upper segment of oesophagus which ends in a blind pouch, with the lower segment attached to the trachea. It should be suspected if the newborn infant has an excess secretion of mucus in his mouth and throat. If allowed to have a feeding he may take the first two or three swallows normally but then regurgitates, chokes, turns cyanotic and may stop breathing. The diagnosis is confirmed by fluoroscopic examination after the introduction of lipiodol, and treatment is surgical.

(d) Diaphragmatic hernia may be congenital and is often associated with a hypoplastic lung on the side of the defect. Symptoms may or may not be present from birth, depending on the amount of bowel that is present in the thoracic cavity causing compression of the lungs. The acute symptoms consist of dyspnoea, cyanosis and evidence of intestinal obstruction aggravated by lying down. The diagnosis is established by radiological

examination; the treatment is surgical and carries a rather high mortality.

INFECTION

Acute infection occasionally causes cyanosis, especially when a severe state of shock and dehydration occurs and stagnant anoxia ensues. Usually, however, there are local and general clinical manifestations of infection so that the diagnosis is rarely confused with other more common causes of cyanosis. Local infection of the lungs or obstruction of the bronchial tree by the oedema and exudate of infections will cause respiratory embarrassment and cyanosis. A generalized septicaemia may cause cyanosis and it may be the first symptom of meningitis, usually due to B. Coli. It may also be seen in Waterhouse-Friderichson syndrome following haemorrhage into the adrenals during a severe meningococcaemia.

CENTRAL NERVOUS SYSTEM

Cyanosis can be caused by direct damage to the respiratory centre by haemorrhage or anoxia, or by compression of the medulla by intra-cranial haemorrhage, cerebral oedema or intra-cranial tumours. Intra-cranial haemorrhage may be traumatic as discussed under birth injuries; it may be a manifestation of haemorrhagic disease of the newborn, congenital syphilis, toxemia, prematurity or congenital blood dyscrasias; or it may be due to anoxia which causes dilatation of blood vessels with oedema and haemorrhage. Symptoms may be present at birth or develop later. They are variable but the diagnosis should be suspected when there is drowsiness, pallor, cyanotic attacks, failure to suck properly, forceful vomiting, anxiety, restlessness, a high pitched cry, muscular twitchings or convulsions. The diagnosis is usually made by lumbar puncture or subdural taps. If no explanation is found by these methods more complex neurological investigation is indicated.

CIRCULATORY

1. Congenital Heart Disease

Cyanotic heart disease may be caused by an insufficient amount of blood reaching the lung as in pulmonary stenosis, by the venous blood being returned directly to the systemic circulation without being oxygenated as in transposition of the great vessels, or by a combination of both factors as in Tetralogy of Fallot.

2. Altered Haemoglobin

Methaemoglobinaemia has been recognized for many years as a cause of enterogenous cyanosis which may vary in degree from a grey tinge to intense navy blue. It may occur as the familial idiopathic type or it may follow exposure to certain drugs or chemicals. Various epidemics and sporadic cases have incriminated nitrates in well water, aniline dyes used for marking diapers, and drugs such as sulphonamides, bismuth subnitrate, aniline derivatives and chlorates. Methaemoglobinaemia should be suspected when there is a family history of "blue babies", when cyanosis occurs in epidemic form, when well water is being used for formulae or when no other cause can be found in an otherwise healthy child. When the diagnosis is entertained, feedings, water, drugs and clothing should be investigated and the blood examined spectroscopically. Methaemoglobinaemia can be treated dramatically with methylene blue but if not diagnosed will lead to a fatal termination.

METABOLIC

Tetany of the Newborn Tetany occuring in the first few weeks of life is of uncertain aetiology. It is usually asso-

ciated with a decrease in the serum calcium level and an increase in serum phosphorous. Clinically, it is characterized by marked hyperirritability, increased neuromuscular excitability varying from twitching to convulsions, and attacks of cyanosis due to laryngospasm. It is often very difficult to differentiate from central nervous system damage.

Investigation and Emergency Treatment

The investigation of a cyanotic baby will be guided by many factors including the type and degree of cyanosis, the time of appearance and the asociated symptoms.

When respiration is not spontaneous at birth the cause is assumed to be anoxic and every effort is made to establish an airway and to provide oxygen. The following principles should be remembered in the resuscitation of the newborn:

Establishment and maintenance of an airway The upper respiratory tract should be suctioned as soon as the head is born and the head should be kept low to give the infant the benefit of postural drainage. Bronchoscopic suction is rarely necessary but may be life-saving in skilled hands.

Oxygen should be provided by a method which controls the positive and negative pressures such as a Mann Resuscitator. Uncontrolled direct pressure will rupture distended alveoli and cause a pneumothorax.

External stimulation may be helpful but should be gentle. Slapping the baby's back, pouring alcohol on its chest or putting a finger in the anus may help to bring about the initial gasp.

Warmth is important as it increases the circulation and prevents shock.

Various drugs have been suggested to stimulate the respiratory centre but they are capable of doing more harm than good and so are only used as a last resort. Of the latter, Coramine and Caffeine and Sodium Benzoate are the most frequently used.

Once respiration is established, the infant should be kept warm in 50-60% oxygen and observed. Nothing should be given by mouth for forty-eight hours. Improvement should be expected by the third or fourth day.

If cyanosis continues or recurs further investigation might include:

(1) Careful physical examination looking especially for pulmonary and cardiac abnormalities
(2) X-ray of the chest
(3) Lumbar puncture and subdural taps
(4) Serum calcium and phosphorous
(5) Spectroscopic examination of the blood
(6) Bronchoscopic or laryngoscopic examination

Conclusion

Cyanosis in the newborn has been discussed with emphasis on the respiratory causes. The combined efforts of the obstetrician, paediatrician and anaesthetist are required to prevent the occurrence, recognize the cause and initiate prompt treatment of cyanotic infants, and thus reduce the number that are found unnecessarily in the neonatal mortality statistics.

Acknowledgment

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GASTRO-ENTERITIS IN INFANCY A SYMPOSIUM

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GASTRO-ENTERITIS is a disease of early infancy, the peak age in one series having been found to be two months. It is rare over the age of 18 months.

The incidence of this disease has been declining steadily over the past 75 years. In 1875, the death rate from diarrhoea in children under the age of five years was 40/1000 population. In New York City, at the turn of the century there were 2000 deaths every summer month because of infantile gastro-enteritis; at present there are less than 200 in a year. With the introduction of prompt and adequate therapy, the mortality has been markedly reduced as well, and at present is reported at between 1%-5% in a number of series. Thirty years ago the mortality was 50%-60%. More severe outbreaks still occur occasionally, and in some epidemics of diarrhoea of the newborn, the mortality has been as high as 40%.

Aetiology

In a small proportion of cases certain specific pathogens may be isolated, e.g. Shigellas and Salmonellas. These produce fairly characteristic clinical pictures and there is general agreement concerning the specific therapy. Entamoeba Histolytica may produce diarrhoea in older children, but it has not been known to do so in infants. Food intoxication, as seen in adults is a rare cause of infantile gastro-enteritis. Other possible causes are over-feeding, allergies to cow's milk protein, coeliac disease, hyperthyroidism, uremia, acidosis, and direct irritation of the bowel by various chemicals.

Parenteral infection as a cause of gastro-enteritis was first incriminated in 1898. In a recent study of 100 cases of gastro-enteritis at the Hospital for Sick Children, 41% were associated with parenteral infections. Usually the infection is fairly mild. The nature of the infecting organism seems to be important, as Streptococcal infections are more commonly associated with gastro-enteritis than are Pneumonococcal infections. Diarrhoea is rare in association with viral diseases. The age of the baby is a deter-

mining factor of considerable significance, as younger babies are much more susceptable to the development of concommitant gastro-enteritis. Prematures are especially vulnerable, and in these babies a mild upper respiratory infection may produce service diarrhoea.

The problem of how these parenteral and gastro-intestinal disorders are related is still not solved. It is possible that the pyrexia and toxemia stimulate the hypothalamus, with consequent disturbance in the sympathetic and parasympathetic systems, and therefore lead to disturbed gastro-intestinal motility. On the other hand, some authorities feel that the majority of diarrhoeal disturbances attributed to parenteral infection are actually secondary intestinal infections which have occurred in infants whose natural resistance has been temporarily lowered by systemic disease.

Gastro-enteritis is much more common in the summer months because of the increase in the number of house flies which disseminate pathogens, and the heat and humidity, which favour the growth of bacteria.

The need of sterile technique in preparing babies' formulae as a prophylactic measure cannot be over-emphasized. Gastro-enteritis is extremely rare in breast-fed infants, presumably because of the absence of contaminating bacteria in the milk. Formulae are excellent culture media for a great many organisms. Babies' gastro-intestinal tracts are very sensitive and contamination of food which would not affect an older child may produce a severe disorder in an infant. Therefore food must be made free of pathogens and properly refrigerated till used. It is practice of this principle which has played a very important part in the decreased incidence of this disease.

Bacteriology

Shigellas and Salmonellas have been mentioned above. In most cases, however, no specific pathogens have been found. Proteus, Paracolon Bacilli and B. Pyocyaneus have been cultured in various cases and incriminated as causative organisms, but the high incidence of these in normals makes assessment difficult. E. Coli, types 0111 and 055 are now considered to be definite pathogens, and have been isolated in a significant number of cases, but there appears to be a high percentage of normal carriers of this organism as well. Some authorities postulate that bacteria which are normally non-pathogenic may under certain circumstances become pathogens. It is possible that the introduction into the gut of any strain of bacteria foreign to it may produce a mild diarrhoea until the host becomes acclimatized.

Recently, a number of investigators have demonstrated viral agents as a cause of gastro-enteritits in infants and also as the specific aetiological agent in epidemic diarrhoea of the newborn.

Clinical Picture

There are two clinical forms—the mild and the severe.

In the mild type the child has 5-6 loose stools per day. The faecal character of the stools is retained at first although there is an increase in the amount of mucus. Later the stools become greenish and there is an increase in flatulence. The appetite remains fairly good, no significant weight loss occurs, and there are no constitutional symptoms.

The severe case may develop from the mild or it may begin suddenly. There is fever, diarrhoea and vomiting, with the rapid development of dehydration, acidosis and shock. Rarely the shock and prostration may precede the diarrhoea. There are more than twenty stools per

day. Faecal charaeter is rapidly lost and the stools are greenish and mucoid. There is marked tenesmus and severe excoriation of the buttocks. Loss of weight may become precipitous up to one pound per day and the temperature may go up to 105-106°F.

With the loss of fluid, the signs of dehydration develop. The skin is gray with diminished elasticity; the fontanelles are sunken, the cranial bones overlap, the eyes are sunken, and the corneas are covered with a mueoid film. The subcutaneous fat feels firm and shotty. Muscle tone is lost. Urinary volume decreases and the NPN begins to rise.

Fever may become quite marked especially in cases of infection with specific enterie pathogens. It is also due to an upset in the heat control eentre because of cerebral dehydration and malnutrition. Other neurological manifestations may develop such as eonvulsions, signs of meningeal irritation, and later, apathy.

As the disease proceeds, shock develops, characterized by eyanosis, cold limbs and a feeble pulse. The skin blanches with light pressure and the colour returns slowly.

Acidosis is eommon in severe diarrhoea and can be reeognized by rapid air-hunger breathing.

Other infections, respiratory, urinary, or cutaneous, may complieate the disease either as the initiating disorder or secondary to the patient's deteriorating state. If the patient is dehydrated, however, the normal inflammatory reaction is in abeyance and the infection may only become evident after the patient has been rehydrated.

Pathological Chemistry and Physiology

electrolyte and fluid losses

Gastroenteritis may produee vomiting, diarrhoea, or a combination of the two. Depending on which of the processes is dominant, metabolic alkalosis or acidosis may result. If vomiting is more severe, the loss of chloride ions will, early in the process, result in metabolic alkalosis. However, since the infant's relatively small glycogen stores are used up quickly, ketosis develops soon after vomiting starts. These acids—acetoacetic and β-hydroxybutyric—are excreted as their sodium salts and therefore alkalosis soon converts to acidosis. More commonly, however, diarrhoea is more prominent than vomiting; and the important ions lost are sodium, potassium, and calcium. This results readily in the produetion of metabolic acidosis.

mechanism of acidosis production

Many factors interact in this process. Sodium, potassium and water are lost in large quantities in the stool. Early in the process the kidney will compensate for this by the selective retention of sodium and H_2O. Since the gut secretions are slightly hypotonic, there will be hyperelectrolytemia and water moves from the interstitial spaces to the intravascular compartment. As this is depleted, the intracellular water will be used up. Again ketosis develops rapidly and when ammoniation by the kidney is no longer adequate to excrete these acids, more Sodium ions are lost in the urine—further aggravating the acidosis. Sodium is also used up in replacing the Potassium lost by the cells which in turn has been used to keep up the falling blood level due to the loss of Potassium in the stools. As the process becomes more severe, circulatory failure occurs resulting in lowered urine output, and, therefore, increased retention of acetoacetic, β-hydroxybutyric, and other acid metabolites. Bicarbonate is also lost in large quantities in the stool. Sinee the ratio of $\frac{H_2CO_3}{HCO_3^-}$ must be kept at $\frac{1}{20}$, the body

tries to compensate for this by over-breathing.

Loss of Calcium in the stool may also lead to post-acidotic tetany.

HYPERPERISTALSIS

The mechanism for this is unknown. In actual infections of the GI tract the inflammatory process may cause painful stimuli; or in gastroenteritis due to parenteral infections, pyrexia or toxemia may act on the hypothalamus which in turn affects the parasympathetic and sympathetic nervous systems to produce hyperperistalsis.

DEFECT IN ABSORPTION

This is due to (a) hyperperistalsis and therefore decreased time for absorption to occur and (b) damage to absorption mechanism itself.

EFFECT ON FAT, PROTEIN, AND CARBOHYDRATE

Fat—poorly digested. This may last for days or weeks after hyperperistalsis has subsided. This is due partly to a decrease in secretions but also to an absorption defect.

Protein—little affected.

Corbohydrate—poorly absorbed as seen by low post-absorptive blood levels.

THE MANAGEMENT OF A MILD CASE

The management of a mild case of Gastro-enteritis can be discussed under the following headings:

(a) Symptomatic Therapy
(b) Investigation
(c) Specific Therapy

SYMPTOMATIC THERAPY

Because of the great danger of dehydration and ketosis in an infant with nausea and vomiting, it is important to treat the child symptomatically immediately. These symptoms may be relieved by removing all the solids from the diet; by removing the carbohydrate from the formula; by diluting the formula, or if necessary by discontinuing the formula and substituting 10% sugar solution. As much fluid should be given as the infant will take and in frequent small amounts, as the feeding is more easily retained. The sugar solution is used to provide maximal sparing of protein, to conserve extra-cellular fluid and to relieve ketosis.

If, after 24 hours, the gastro-enteritis is subsiding, the infant can be put on ½ strength skim milk formula or ½ strength protein milk for 2-3 days and if there is no further upset, the regular formula can be resumed. The solid foods are gradually added leaving the addition of fruits until the last. If at any time the diarrhoea recurs, a second period on sugar solution and then a step-wise increase in the strength of the formula from a basic value of 10 cal./lb. by 10 cal./lb. every 2-3 days. Caloric and fluid intake is maintained by feedings of water and sugar solution.

Only about 1% of the cases of Gastro-enteritis occur in breast-fed infants but when it does occur, it can be treated by substituting sugar solution for 1 or 2 of the breast feedings and then gradually returning to the breast feeding as the stools become less frequent and more formed.

Other preparations (e.g. Casec) can be added to the feeding to increase the protein intake if necessary.

Compounds containing kaolin, aluminum gel and pectin are used to treat the diarrhoea, but these are not too satisfactory. They absorb fluid containing minerals, vitamins and amino acids and, although the stools appear formed, there is a false sense of security as to the condition of the infant. Tincture of Camph. Co. can be given after every loose bowel movement providing the infant is not vomiting.

INVESTIGATION

1. Complete History including onset of symptoms, appearance of stools, type of vomiting and appearance of the vom-

itus, previous infections of patient or family, feeding history, family history of allergies.

2. Complete Physical Examination.

3. Urinalysis including microscopic.

4. Blood Examination—haemoglobin estimation, W.B.C. count.

5. Stool Examination and culture.

Usually the cause of the intestinal upset becomes very obvious from the history or physical as the commonest cause in infants is secondary to infection usually in the upper respiratory tract. Other tests are carried out, if found necessary by findings in the history or physical examination.

SPECIFIC THERAPY

The specific therapy will depend on the cause of the enteritis and its severity.

For an U.R.I., Trulfa 1 gr./lb./day for 3 or 4 days may be sufficient. Penicillin can also be given with the Trulfa if the infection is severe.

If a specific enteric organism is cultured, the patient should be isolated and treated with specific antibiotics.

Terramycin } oral: 5mg/lb q.6.h.
Acromycin } I.V.: 3mg/lb q.12h.
Neomycin—oral: 5-10mg/lb q.6.h.

Neomycin is also sold in combination with Kaopectate which is frequently used.

Chloromycetin
oral 10-12mg/lb q.6.h.
I.M. 65mg/lb/day
I.V. 7mg/lb/q.6.h.

Occasionally, the diarrhoea and vomiting will stop when the milk formula is discontinued and reappear when milk is added to the feeding. When there is no apparent cause for the gastro-enteritis, it is believed to be due to a milk allergy and a Mullsoy or Nutramigen formula is prescribed.

Throughout the treatment of a mild case of Gastro-enteritis, the infant should be carefully watched for signs of dehydration, in which case the patient should be hospitalized and I.V. therapy begun.

MANAGEMENT OF A SEVERE CASE

RESTORATION OF KIDNEY FUNCTION

Given sufficient water to work with, the normally functioning kidney can adjust the electrolyte balance and correct mild acidosis. As normal saline is more concentrated in respect to chloride than physiological saline, a diluted solution such as ⅔ 5% Glucose and ⅓ N saline is very useful. 3 ounces of fluid per pound body weight per day with a maximum of 40 ounces (1200 cc) satisfies the daily needs and if the baby is not eating or not absorbing its feedings then this amount must be given intravenously. It is given at the rate of 75-100 cc per hour or faster until the general condition improves and then at 30-50 cc per hour. Whether more fluid is given depends on the clinical state, as determined by the disappearance of shock, restoration of urine volume, cutaneous turgor and body weight.

The glucose content in "⅔ and ⅓" is sufficient to combat ketosis but is not an attempt to provide a normal caloric intake.

TREATMENT OF SHOCK

If shock still persists after 200-300 cc of fluid have been given, a blood transfusion of 5-10 cc per pound body weight running at 30-50 cc per hour is given. Plasma is used if blood is not available.

CORRECTION OF ACIDOSIS

Enthusiasm has waned for the use of intravenous alkali in the correction of acidosis because of the danger of producing tetany if over-correction occurs, or if there is too rapid correction, even when the pH is not pushed to the alkaline side. Very severe acidosis may cause convulsions and even death, but a CO_2

Combining Power of 20 or over per se has been found to cause no serious metabolic dysfunction, and correction of the acidosis alone produces no clinical improvement other than the disappearance of dyspnoea. Therefore there is an increasing tendency to rely chiefly on the restoration of renal function and provision of adequate electrolytes to correct the acid-base balance. However, if the CO_2 Combining Power is known to be less than 20 volumes %, or if the patient is clinically very acidotic with rapid deep respirations, an ashen-grey colour, and an anxious expression, then an alkaline solution, usually ⅙ M Sodium Lactate, is given according to the formula: Vol. of alkali in cc =

$$\frac{(50 - CO_2 C.P.) \times 0.8 \times \text{wt. in lbs.}}{2}$$

(If CO_2 C.P. is unknown, use 20 if clinically very acidotic.) Repeat if necessary.

If post-acidotic tetany occurs give 10 cc of 10% Calcium Gluconate intravenously very slowly over a 5 minute period. This is repeated in 4 hours if necessary. Anti-convulsants may be required and hyperpyrexia is controlled with sponge baths, cool enemas, etc.

POTASSIUM THERAPY

The blood Potassium level is often low, and as the dehydration is corrected the level falls farther still and, when severe, results in muscular weakness, abdominal distention, mental changes (apathy or delirium) and ECG changes. However intravenous Potassium therapy should not be started until renal function is restored, since there is a narrow margin between the normal levels of blood Potassium and the level at which complete heart block or even cardiac arrest occur. The oral route is much safer and as soon as the patient is conscious he should be offered diluted orange juice or a solution of 2 parts Sugar Solution and 1 part Darrow's Solution in small amounts frequently (1-3 ounces every 1-3 hours).

When the urine output is normal, there is a wide margin of safety in intravenous potassium administration, and so if the patient is still unable to take liquids by mouth, Darrow's solution may be given fairly safely—40 cc per pound per day at 40-50 cc per hour.

COMMENCEMENT OF ORAL FEEDINGS

There are two schools of thought at present.

One school represented by Chung and Holt believes that food is not harmful during severe diarrhoea and may even be beneficial since *some* of it is absorbed and thereby increases the caloric intake. They offer an initial feeding of glucose to see if the baby will vomit, and if he tolerates it they offer standard feedings at the usual intervals, ignoring the increase in frequency and bulk of stools. They emphasize, however, that the feedings are to be used as a supplement to, and not as a substitute for intravenous feedings.

The most prevalent view is that food is harmful during severe diarrhoea. For the first 12-24 hours the baby is receiving intravenous fluids and nothing by mouth, and, then, as his condition improves he is offered Sugar Solution in small amounts (1-3 ounces every 1-3 hours). After 2-3 days he is offered diluted milk feedings supplying 10 calories per pound per day and this is increased by 10-20 cals per pound every 2-3 days if tolerated. 1-2 Gms KCl may be added to the formula per day if orange juice is not tolerated. Rice cereal, then meat, and finally fruit are added

until the baby is on his normal diet. The fruit is added last because it is most likely to aggravate the diarrhoea. The intravenous fluids are continued as the food is added and are stopped only after one is certain that the baby is absorbing sufficient fluid from the GI tract.

Acknowledgment

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THE PRIMARY COMPLEX

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THE primary portal of entry of tuberculosis is the lung. Other sites of primary infeetion do occur, such as the tonsils and gastrointestinal tract, but in this country they are rare. The reaction to this infection in children is designated as the primary complex. However, if the primary infection occurs at a later age, the pulmonary reaetion is often different, and exudative pleuritis has a predominant position as the primary manifestation. The usual course is the non-progressive primary complex, whieh can be detected clinically by the development of tubereulin hypersensitivity. In a small percentage of cases, however, early post-primary progression does oecur: consequently these children must be watehed closely.

The *mode* of infection when the primary site is the lung is by the air born route. Infected patients expectorate many contaminated droplets. The larger droplets do not remain air born for long periods, and have greater diffieulty reaehing the finer bronchi and alveoli. It is the smaller droplets eontaining only a few bacilli, which are the main culprits. This supports the view that the initial infeetion is minimal and is of value in the development of immunity.

If allergy is defined as an altered type of reaction to an agent, produced by a primary reaction to the same agent, then hypersensitivity represents as increased intensity of reaction and immunity a decreased intensity, which gives increased resistance. The hypersensitivity appears at the end of the incubation period, and modifies the primary focus by producing a non-specific peri-focal serocellular exudate. A high degree of hypersensitivity is probably a disadvantage in that the primary infection will be larger by virtue of the non-specifie reaction and the post-primary disease may show adverse developments as for example, the sequestration of a large infiltrate in the nature of a local Arthus phenomenon. In animals it is possible to desensitize without loss of specific immunity, by injecting repeatedly larger doses of tuberculin, but it is not known if this is possible in the human. Simultaneous with the development of tuberculin sensitivity acquired speeifie resistance is also attained by the individual. This immunity confers an increased resistance to new infections by inhibiting

the multiplication of the bacteria and preventing their penetration and activity by proliferative reactions. There does not seem to be any close parallel between the degree of hypersensitivity and immunity. The acquired immunity is most effective against fresh exogenous infections having little or no activity against the tubercle already present in the primary focus. However reinfection is most important in that it reactivates the primary or metastatic foci already present in the body. This has been referred to as exogenous activation of an endogenous reinfection.

The human is extremely sensitive to the tubercle and probably one bacillus can initiate the primary complex. The oragnisms find their way to the terminal bronchioles and set up an acinar nonspecific pneumonitis. A peri-focal and centripetal lymphangitis occurs early and the bacteria are carried to the regional tracheobronchial lymph glands. This reaction occurs rather quietly for three to eight weeks at which time there is the development of tuberculin sensitivity. The primary focus is now altered by the outpouring of serous cellular fluid and caseation occurs at the hilar nodes as well as a mild hilitis. The exudate surrounding the primary focus is referred to as the primary infiltrate *The primary focus, centripetal lymphangitis, and the caseous regional nodes together constitute the primary complex.*

Clinically the majority of primary infections are silent or cause short noncharacteristic symptoms indistinguishable from an ordinary respiratory infection. The most common clinical sign is fever which is usually slight and transient and in no way characteristic. A very rare and lethal form is characterized by high fever, cyanosis and tachycardia and was described by Landouzy as typhobacillosis. This represents a tuberculous bacteremia and toxemia allowed by a state of anergy, i.e. complete impotence of reaction as might be seen in agronulocytosis or leukemia. Occasionally there are signs of bronchial compression by enlarging nodes such as a brassy cough, pain or dyspnea. Rales are not heard in uncomplicated cases.

The *diagnosis* must be suspected and a tuberculin test performed in all febrile illnesses. It is generally agreed that a negative reaction to 1 mg. of O.T. which has been injected intracutaneously excludes tuberculosis except under the following circumstances: (1) the test is made in the incubation period, (2) the patient is suffering from an acute anergic type of infection for instance, acute military tuberculosis, (3) during certain acute febrile illnesses such as measles in which case there may be a temporally decreased sensitivity to tuberculin. A positive test indicates that the child has tuberculosis or has had it or has received a B.C.G. inoculation.

On *roentgen examination* the primary focus has a subpleural location, usually in the right middle lung field which has the shortest bronchial pathway. It is seen as a more or less rounded macular shadow. The characteristic point is that it is unilateral and bipolar, the two poles being connected by a band of shadow, representing the centripetal lymphangitis. The primary infiltrate must be differentiated from the so called "early infiltrate". This latter infiltrate has a different prognostic significance in that it represents a definite landmark on the roadway to pulmonary phthisis or tertiary tuberculosis. Resorption of the primary infiltrate with *restitutio ad integrum* is the rule but the early infiltrate commonly breaks down with cavernous liquefaction and leads to further intracanalicular dissemination. It usually appears as a round, somewhat cloudy, poorly delineated, solitary macular shadow with a predominent apical or in-

fraclavicular localization. Its mode of origin is somewhat obscure but it is often hematogenous or it may represent bronchogenous spread from the breakdown of a subprimary focus. In some cases it is due to exogenous reinfection.

The usual *course* of the primary infection is with resorption of the primary infiltrate and encapsulation of the primary focus by connective tissue and subsequent apitite impregnation of the caseous center. Complete involution in a calcific node requires several years. The presence of these calcific masses signifies a healed primary complex. Complete healing is not always attained and mild lymphogenous spread may persist for several years. This is usually manifest by spread along the tracheobronchial glands and assumes the clinical aspect of hilar gland tuberculosis. Progression of the primary complex may also ocur by hematogenous dissemination. If this occurs early, acute miliary tuberculosis with or without meningitis will develop, but if this occurs at a later date, discrete pulmonary and extrapulmonary metastases are more likely.

Bronchial tuberculosis occasionally occurs. This can be defined in the clinical sense as all tuberculous processes of the bronchial wall which alter the symptomatology and thus indicate the need for special therapeutic procedures. The "epituberculous" infiltrate is an example of this. Bronchial obstruction at first produces an emphysema, but once the occlusion is complete, the air is rapidly resorbed with atelectasis of the lung supplied by that bronchus. This usually occurs in the paravertebral pulmonary segments, especially in the upper lobes. With fibrosis of the compressing nodes and relief of obstruction, this area usually re-expands readily. The danger is that certain specific and non-specific processes may be masked by this atelectatic area. As a result of edema, induration may occur and prevent re-expansion, or the fibrosis may result in localized traction bronchiectasis. Hematogenous dissemination or intracanalicular extension of the tuberculous process may also occur, but healing is favoured in this passively hyperemic field.

In considering the *management* of these children it must be remembered that the usual course is healing of the primary complex without sequelae. Chemotherapeutic agents have value in tuberculosis in that they can arrest malign developmental activities and bring hematogenous dissemination to an earlier end. The essential developmental processes cannot be altered. Therefore the treatment in the uncomplicated case is careful watching so that drug therapy can be instituted early if progression or postprimary disease is observed. The uncomplicated primary complex only requires symptomatic treatment such as bed rest or nothing at all except careful watching, depending on the severity of the symptoms.

ABSTRACTS

"Three Months' Colic": R. S. Ilingworth; Archives of Diseases in Childhood, **29**, 165, 1954 (June).

The term "three months' colic" is reserved for a clinical condition in which the baby in the first three months of life has rhythmical screaming attacks in the evenings, which are not stopped when he is picked up, and for which there is no logical explanation. Crying can be easily ascribed to colie when it actually

is due to some readily correctable cause, such as hunger. The severe forms are thought to be so characteristic that they cannot be confused with anything else. The literature on the subject is reviewed.

A controlled investigation of colic was carried out using 50 babies with colic and 50 who did not not have colic. It showed that mothers of the two groups did not differ as regards their age, parity and pregnancy history. The babies differed in no way as regards their sex, birth weight, feeding history, family history of allergy, signs of allergy, number of stools, or weight gain. They appeared to be well, normal babies, apart from their attacks of pain in the evenings, and when followed up, they continued to be normal.

The colic began in the first 15 days of life at 5 p.m. or later in the evening. Colic disappeared at an average age of 9½ weeks—54% having lost it by the end of 2 months.

The cause of colic, in the light of the above findings is discussed. It is felt that it is not due to underfeeding, overfeeding or other errors in feeding technique, or to mismanagement, spoiling, hypertonia or swallowed air.

X-rays taken during attacks of colic did not show excess gas in the bowel. The author feels that this colic is most likely due to local obstruction to the passage of gas in the colon by local spasm or kinking of uncertain cause. No explanation is offered for the predominant occurrence of colic in the evenings.

I. G. L. Van Praagh

New Theory Concerning the Mechanism of the Initiation of Respiration in the Newborn: S. Jäykhä: Acta Paediatrica 43, 399–410, (Sept. 1954).

This age old problem is reviewed by Dr. Jäykhä and on the basis of preliminary experimental procedures he has advanced what he believes is a new concept of neonatal respiratory expansion; namely that "expansion of the pulmonary alveoli is caused by capillary erection which is effected by the initiation of the pulmonary circulation".

On the basis of clinical observations of lung expansion in the presence of congenital laryngeal atresia, etc., a new theory seemed necessary. He began to think in terms of pulmonary circulation which from pre- and post-natal post mortem sections, had been seen to increase many fold along with associated alveolar expansion. According to classical thinking external air insufflation ex- According to Jäykhä these latter act pri- pands alveoli with secondary closure of the ductus arteriosus and foramen ovale. marily in "preventing the initiation of blood flow and the increase of blood pressure in the pulmonary circulation" in utero with resultant amniotic fluid aspiration and come to act only after birth where their closure is primary in allowing capillary congestion, erection and subsequent alveolar expansion.

This hypothesis is supported by experimental arterial injection of macrodex into the pulmonary artery of excised lungs under controlled conditions. He found that the vital capacity is much increased, microscopic sections revealed expansion, and lungs subsequently floated on water. The experiment failed in "premature" lungs. He hypothesized that the endothelium and epithelium of lungs had to be "mature" to allow this "erection".

He emphasizes that this is merely a preliminary report of a theory supported by early yet dramatic evidence.

D. W. Wilson

Endocardial Fibroelastosis in Infancy: O. Mortensen, F. Kissmeyer-Nielsen and P. Kolle-Jorgensen: Acta Paediatrica, 43, 87, 1954.

This disease is characterized by a non-inflammatory thickening of the endocardium with cardiac enlargement. There

is predominantly involvement of the left side although the thickening may be generalized. Concurrent myocardial hypertrophy may also be present. Histological examination reveals an inerease of the fibroelastic tissue and ground substance of the endocardium with minimal changes in the myocardium.

The aetiology of the disease is obscure but several theories have beeu proposed. It has been regarded as a developmental error of mesenchymal tissue or a direct result of anoxia occuring in the antenatal period. An anomalous origin of the coronary arteries has been noted in several cases and this lends support to the latter theory.

The disease is essentially diagnosed by pathological examination but certain symptoms are suggestive enough to allow a tentative diagnosis. The disease may present suddenly and be rapidly progressive with death in one or two days or it may be milder with reeurrent episodes of symptoms. Ninety per eent of children having the disease are dead by the age of two.

Those presenting the acute picture are usually under six months of agc. A period of good health is interrupted by the sudden onset of dyspnoca, cyanosis, and taehycardia. Those that show the milder form have rccurrent episodes of similar symptoms with periods of apparent recovery. The most important sign is eardiac enlargement. This is usually accompanied by cyanosis, dyspnea, and enlargement of the liver. A soft apical systolie murmur is occasionally heard.

Roentgen examination always reveals an enlarged heart which may be globular in shape and often is suggestive of pericardial effusion. In order to make a diagnosis one must exclude rheumatic fever and myocarditis.

Three case histories and a discussion of the histological changes are presented and discussed by the author.

J. D. Ainslie

OF CURRENT INTEREST

ONWARD AND UPWARD

During the last few weeks we have had many inquiries regarding the demise of the Medical Reading Room. Perhaps many do not realize that the medieal eolleetion has joined forees with the scienee seetion to become the Seienee and Medieine Division of the University Library. Service in the Medical Reading Room was suspended for three days during the move of the 50,000 volumes. With the offieial opening of the Humanities Division in the new building on November 26th, Seience and Medicine took over the old building. Now scientifie and medical books and bound journals circulate from the Central Desk in this section. Owing to the fact that many of the science books are in departmental libraries, about two-thirds of the eirculation in this division is medical. As an encouragement to profitable browsing, each medical student is now entitled to a stack pass—the eatalogue is not always the answer. The medical books are on the first and second floors of the stacks.

There are two very spacious reading rooms; one a general reading room, and the other a current periodical room. Over 400 current medical periodicals are received in this seetion. The indiees to

this new material, e.g. Index Medicus and Current List are kept in the Medical Reference Section of the hall.

In 1927 when the medical books were transfered to the Medical Reading Room from the main stacks there were about 15,000 volumes. Since that time the collection has grown to approximately 35,000 bound periodicals and 15,000 monographs. In a recent survey of medical school libraries, by the Medical Library Association, we were very gratified to find our collection ranked among the first ten on this continent.

We hope that you will find the new quarters more pleasant and less distracting that the old, and will always ask for any help we can give in the use of this valuable collection. Please do not hesitate to ask for the medical librarian.

MARY GALT, *Librarian*
Science and Medicine Division

FACULTY NOTES

Professor R. M. Janes has recently been elected President of the Canadian Association of Clinical Surgeons.

Sir James Learmonth, Professor of Surgery at the University of Edinburgh, recently visited the Faculty of Medicine as the Sir Arthur Sims Travelling Professor of the Royal College of Surgeons of England.

Medical Alumni Association Bursaries have been awarded to Miss M. G. Norman, J. H. Chizen, T. Izukawa, Mrs. M. L. Cohen. Other awards in the Faculty are the Charles E. Frosst Scholarship — G. S. Cohen; the B'nai B'rith Scholarship — M. Berger; the Baptie Scholarship—D. Glick.

The Reeve Prize has been awarded to Dr. A. Miller of the Department of Psychiatry for his monograph entitled "Lobotomy—A Clinical Study".

NEW MEDICAL BOOKS

NEW MEDICAL ACCESSIONS

December 17/54—January 10/55

Arey, L. B.: **Developmental anatomy.** 6th ed. 1954.
Conybeare, J. J.: **Textbook of Medicine.** 11th ed. 1954.
Nelson, W. W.: **Textbook of Pediatrics.** 6th ed. 1954.
Anderson, W. A.: **Pathology.** 2nd ed. 1954.
Foote, R. R.: **Varicose veins.** 2nd ed. 1954.
Jensen, J.: **Modern concepts in medicine.** 1953.
Selye, H.: **1st annual report on stress.** 1951.
Laborde, S.: **Le promlème du cancer.** 1951.
Ballenger, H. C.: **A manual of otology, rhinology and laryngology.** 4th ed. 1954.
Bromberg, W.: **Man above humanity; a history of psychotherapy.** 1954.
Cullen, E. C.: **Anesthesia in general practice.** 4th ed. 1954.
Wolff, E.: **The anatomy of the eye and orbit.** 4th ed. 1954.

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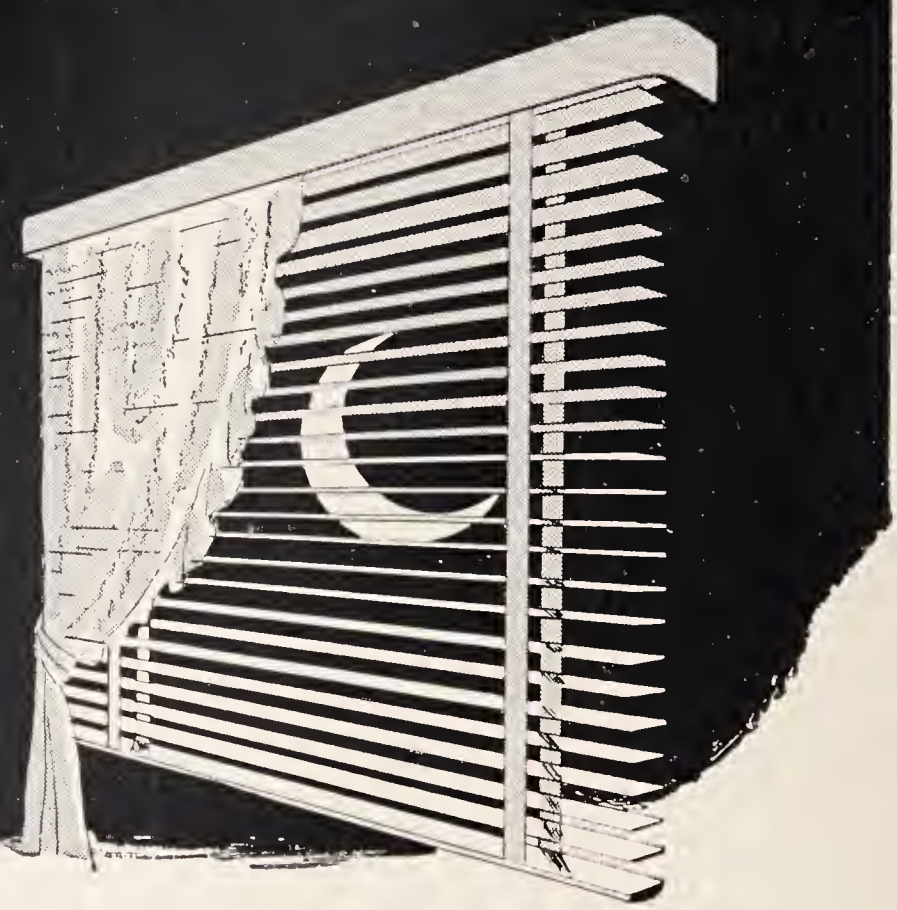

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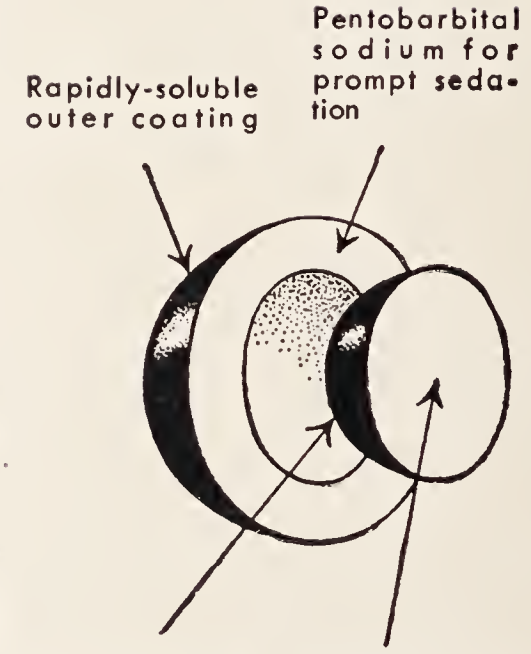
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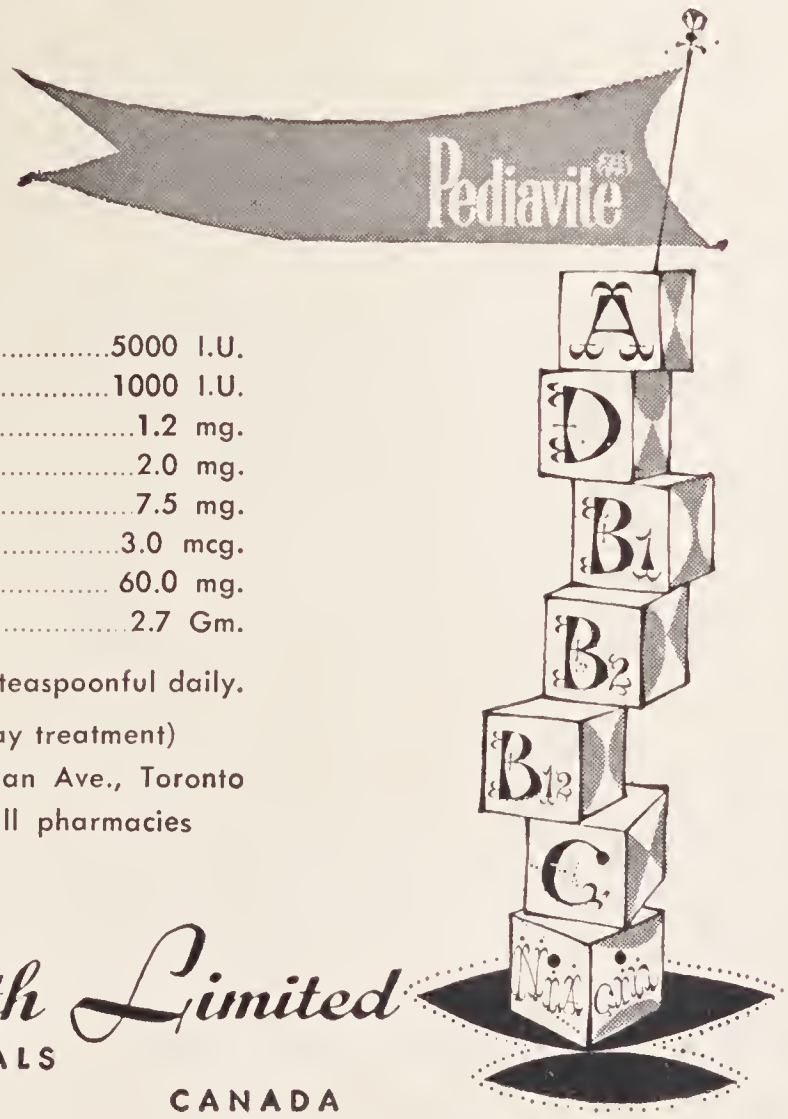

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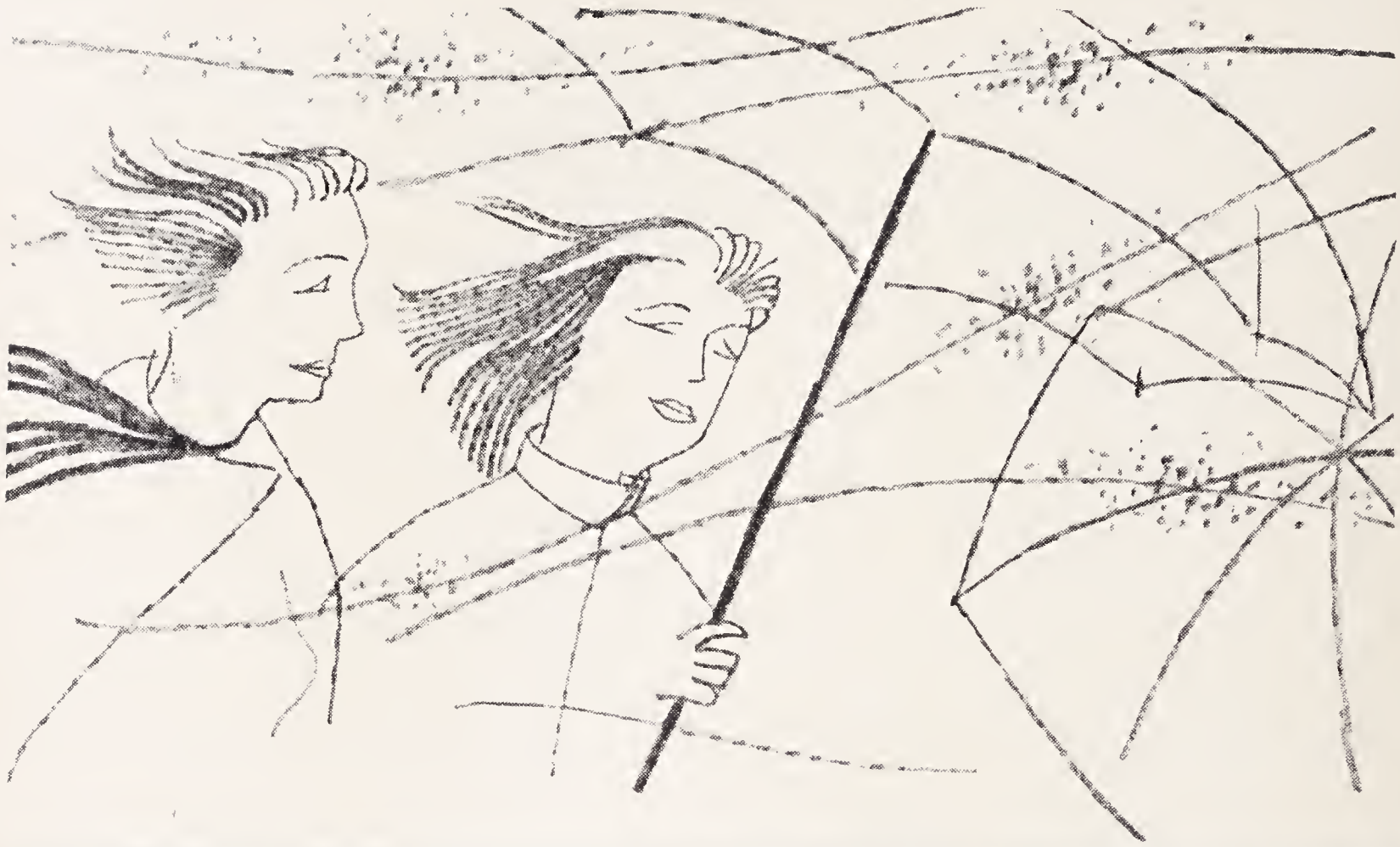

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